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Management of Uterine Fibroids

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted multiple Key Informants who represent the end-users of research. The EPC sought Key Informant input on the priority areas for evidence synthesis and research**.** Key Informants are not involved in the analysis of the evidence or the writing of the report**.** Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows:

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted a group of technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Management of Uterine Fibroids

Structured Abstract

Objectives. We assessed the evidence about management of uterine fibroids. Specifically, we sought to determine effectiveness of interventions, risks of harm, and whether individual or fibroid characteristics influence outcomes.

Data sources. We searched MEDLINE® via PubMed® and EMBASE to identify publications, as well as reviewed the reference lists of included studies.

Methods. We included studies published in English from January 1985 to March 2015. We identified randomized clinical trials to assess outcomes and harms of interventions. We used data from trials in a meta-analysis to estimate likelihood and timing of subsequent interventions for fibroids based on initial type of intervention. To describe risk of cancer dissemination from power morcellation, we included studies that allowed calculation of prevalence of sarcoma, in what were believed to be fibroid tissue, and those that included prospective data about outcomes when sarcomas were discovered. We extracted data, assessed risk of bias, and rated the strength of the evidence for informing care.

Results. Of 90 included studies, 40 studies assessed medications, 25 assessed procedures, and 36 assessed surgeries. Among medications, GnRH agonists and mifepristone improved fibroid-related symptoms like bleeding and reduced fibroid size. Several other medications may have promise but are not supported by sufficient evidence. Uterine artery occlusion and high intensity focused ultrasound (HIFU) are effective for decreasing the fibroid size/volume. Few other outcomes are well investigated for HIFU or ablation techniques. Uterine artery embolization studies demonstrated improved bleeding, pain, and quality of life outcomes. Myomectomy reduced fibroid volume and improved quality of life, but did not improve bleeding. Hysterectomy (i.e., removal of the uterus) resolves bleeding and bulk symptoms and improved quality of life. Few well-conducted trials directly compared treatment options. Subsequent intervention ranged from zero to 40 percent in studies that followed women after initial fibroid treatment. Subsequent intervention rate were lowest for initial medical management at two years followup; higher for myomectomy and UAE especially among younger women. No individual characteristics of women or their fibroids were definitely associated with intervention benefits or patient satisfaction; however these findings were limited by availability of few, small studies. We estimated that 3 to 10 women out of 10,000 surgeries will have a sarcoma at the time of surgery from data in 147 studies. Analysis of survival data suggested that use of morcellation and morcellation method were not strong predictors of overall survival.

Conclusion. A range of interventions are effective for improving symptoms and quality of life, most with low to moderate strength of evidence. No intervention that leaves the uterus in place is definitively superior. The probability of subsequent intervention two years after initial fibroid treatment varies widely, with greater variation among younger women. The risk of encountering a sarcoma at the time of fibroid surgery is low and the method of fibroid tissue removal does not appear to determine survival. Evidence to guide choice of intervention is likely best when applied in the context of individual patient needs and preferences.

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Executive Summary

Introduction

Most women will develop one or more uterine fibroids during their reproductive lifespan.[1] In the United States, an estimated 26 million women between the ages of 15 and 50 have uterine fibroids.[1-4] More than 15 million of them will experience associated symptoms or health concerns.[5,6] The personal and societal costs of diminished quality of life, disruption of usual activities and roles, lost work time associated with symptoms, and healthcare expenditures are substantial. Including all types of interventions, direct annual healthcare costs in the United States are projected to exceed $9.4 billion.[7] Lost wages, productivity, and short-term disability are estimated to total more than $5 billion, perhaps as much as $17 billion, with roughly $4,624 in costs per women in the first year of diagnosis.[7,8]

Treatment options differ in fundamental aspects such as cost, invasiveness, recovery time, risks, likelihood of long-term resolution of symptoms, need for future care for fibroids, and influence on future childbearing. Thus synthesis of available evidence is crucial to assist women and their care providers in making well-informed and personalized decisions.

Scope and Key Questions

To inform clinical decisions about care we focused on evidence from randomized controlled trials (RCTs) that assess effectiveness of currently available interventions for women of any age with fibroids. We also sought to identify factors that might influence likelihood of favorable results or harms from treatments. We included studies evaluating medications, procedures, and surgeries for the management of uterine fibroids. We considered more invasive interventions that require at least a brief hospital stay as surgical and interventions that typically can be conducted in an office or as same-day surgery as procedures.

We also summarized data from women who were followed within trials without active intervention. In light of recent uncertainty about the risk of cancer dissemination following morcellation of fibroids during minimally invasive procedures, this review also includes literature about morcellation and risks of leiomyosarcoma.

Key Questions

Key Question 1. What is the comparative effectiveness (benefits and harms) of treatments for uterine fibroids, including comparisons among these interventions?

Key Question 2. Does treatment effectiveness differ by patient or fibroid characteristics (e.g., age, race/ethnicity; symptoms; vascular supply to fibroids; menopausal status; or number, size, type, location, or total volume of fibroids)?

Key Question 3. What is the risk of encountering a uterine sarcoma when morcellation is used for masses believed to be uterine fibroids at the time of myomectomy or hysterectomy?

Key Question 4. Does risk of sarcoma dissemination differ by patient or fibroid characteristics (e.g., age; race/ethnicity; symptoms; menopausal status; imaging characteristics; vascular supply to fibroids; or number, size, type, location, or total volume of fibroids) or surgical approach to morcellation?

Methods

We searched MEDLINE® via PubMed® and EMBASE to identify publications in English from January 1985 to March 2015. We also checked the reference lists of included studies. We dually reviewed each publication against *a priori* inclusion/exclusion criteria. For KQ 1 and KQ 2, we identified RCTs to assess benefits or harms of a medical, procedural, or surgical intervention compared with an inactive control, including expectant management, placebos, or alternate intervention. Eligible studies for KQ 1 or KQ 2 had to report one or more patient-centered outcome at baseline and in followup (e.g., symptom improvement, blood loss, pain, quality of life). We did not include studies reporting intermediate outcomes only and did not include studies designed to demonstrate technical merits of different procedures.

We extracted data, assessed risk of bias, and rated the strength of the evidence for informing care using standard AHRQ systematic review methods. We used follow up data across all trials that included subsequent treatment to estimate probabilities of selecting subsequent treatment. The probability of the occurrence of subsequent treatment events was estimated using a Poisson model, where the rate of occurrence was assumed to be a function of patient age and study followup time, on a logarithmic scale.

To understand risk of sarcoma and the influence of morcellation (KQ 3 and KQ 4) we conducted dual review and data extraction from nonrandomized cohort studies and observational studies. For KQ 3, we structured a search to encompass the papers included in a 2015 review and meta-analysis[9] that estimated the prevalence of LMS among tumors presumed to be fibroids. We updated the search, used comparable eligibility criteria, and calculated new estimates for the prevalence of sarcoma identified at the time of surgery for presumed fibroids including both the prior studies and newly identified papers. To be included, papers were required to provide data to calculate the proportion of myoma or uterine specimens found to include leiomyosarcoma. Eligible studies also had to require histology of tumors from all patients both those with benign and malignant pathology findings. We calculated meta-estimates of the probability of sarcoma for all relevant studies and by study characteristics. Additionally, our model included the effect of the mean age of women in each study arm, as a potential covariate.

For KQ 4 we did a broad search and reviewed potentially eligible papers for those that included data about sarcoma diagnosis and survival as well as the proportion of women exposed to use of power morcellation who were subsequently diagnosed with disseminated sarcoma (meaning presence or recurrence of sarcoma beyond the initial operative tissue specimen). We extracted data to allow comparison of those for whom power morcellation was not used and the uterus was removed intact or sharp morcellation with a scalpel was performed. We generated Kaplan-Meier survival curves using event times when they were made available and imputing them when they were not published, in order to compare survival time by method of surgical removal of the specimen.

Results

The first AHRQ systematic review on the management of uterine fibroids was published in 2001 and included 30 randomized trials of interventions to treat fibroids.[10] A more recent AHRQ review in 2007[11] identified 29 trials. Most were judged to be of poor quality and had abbreviated followup of outcomes. Outcomes typically focused on technical success of the intervention. Measures of quality of life, improvement in symptoms and satisfaction with care outcomes were relatively rare. These reviews served to answer key questions about epidemiologic correlates of

fibroids, to demonstrate lack of evidence about natural history of disease, provided models of lifetime incidence and need for treatment and included cohort studies as a surrogate for trials to examine preliminary evidence of effectiveness and predictors of outcomes.

In the intervening years, the literature has grown to include 109 publications from 90 unique trials. Newer studies have been of somewhat higher quality – 15 in this report were judged good quality trials, 27 fair, and 48 poor quality. More interventions have been assessed for longer follow-up periods, up to 5 years. Patient-reported outcomes are more common, reported in 60 percent of studies, as is data to determine what sequences of interventions are most likely to be chosen subsequently by women with reference to their prior treatment allocation in trials (48 studies). More trials also provide more data to examine whether particular desired outcomes are more likely to be achieved among women with specific characteristics. Six studies provided information about factors such as age, menopausal status, and fibroid characteristics that may modify outcomes or risk of adverse events.

Clinical trials are not a practical vehicle for examining exceptionally rare harms. To address the current pressing concerns of potential for cancer dissemination at the time of surgery for fibroids, we identified a separate literature of 147 publications to examine risk that a mass believed to be a fibroid was found to be a sarcoma. We also sought data within 17 papers that allowed estimation of the risk of progression of sarcoma by type of morcellation used, estimating aggregate mortality by surgical methods used. Lastly, we combed these papers for data about whether characteristics of women or their fibroids could be linked to greater or lesser association with sarcoma in the time following exposure to use of morcellation during a surgery for fibroids.

KQ 1: Comparative Effectiveness of Treatments for Fibroids

Studies provided information on effectiveness more commonly than harms. We summarize our results below by category of intervention, providing data about adverse events when available and statistically informative. We categorized interventions using the publication authors' description. Interventions include hysterectomy via abdominal, vaginal, laparoscopic, or robotic approach; myomectomy via laparotomy, laparoscopy, hysteroscopy, or robotic approach; uterine artery embolization including ligation and occlusion; ablative procedures (e.g., MRgFUS, cryoablation, radiofrequency); progestin-containing intrauterine devices; medications to improve or resolve symptoms or reduce size of fibroids; and expectant management or placebo.

Evidence Map for KQ 1

We summarize the number of studies reporting final health outcomes, number of participants and duration of followup for medication (Table ES-A), procedural interventions (Table ES-B), and surgery (Table ES-C). The complete list of outcomes reported, measurement tools, duration of treatment, and will be publicly available in the Systematic Review Data Repository.

Table ES-A. Final health outcomes reported in medication studies

Arm Class	Outcome Category	Studies Reporting	Sum Baseline N	Mean followup duration	Followup Months, SD
GnRH agonists	Symptom status	13	3977	9.6	3.9
	Sexual function	2	315	12	0
	Fibroid characteristics	17	1058	8.9	3.5
	Subsequent treatment for fibroids	2	89	18.8	17.2

Arm Class	Outcome Category	Studies Reporting	Sum Baseline N	Mean followup duration	Followup Months, SD
LNG-IUD	Symptom status	1	60	6	0
Other Medications (cabergoline, tranexamic acid, tibolone)	Symptom status	5	186	5.5	3.3
	Fibroid characteristics	5	166	6.6	4.8
	Subsequent treatment for fibroids	1	30	1.5	0
Progestins (mifepristone and ulipristal)	Symptom status	10	8737	7.3	5
	Pregnancy outcomes	2	270	7	2.8
	Sexual function	6	668	9	5.3
	Fibroid characteristics	10	3043	7.5	4.8
	Subsequent treatment for fibroids	3	721	6.1	2.8
Estrogen Receptor Modulators and Antagonists (raloxifene and tamoxifen)	Symptom status	3	312	7.5	2.6
	Fibroid characteristics	4	380	6.6	2.3
	Subsequent treatment for fibroids	1	10	60	0

Abbreviations: GnRH= gonadotropin-releasing hormone; LNG-IUD= levonorgestrel-releasing intrauterine device; N=number of participants; SD= standard deviation

Table ES-B. Final health outcomes reported in procedural studies

Arm Class	Outcome Category	Studies Reporting	Sum Baseline N	Mean followup duration	Followup Months, SD
HIFU	Symptom status	1	33	12	0
	Sexual function	1	384	6	0
	Fibroid characteristics	3	433	2	3.8
UAE	Symptom status	14	3535	9	8
	Fibroid characteristics	11	1336	9	8.7
	Subsequent treatment for fibroids	10	975	12.3	7.4
	Satisfaction with outcomes	5	158	6	3
Uterine artery occlusion and coagulation	Symptom status	3	399	5.8	0.7
	Fibroid characteristics	1	160	6	0

Abbreviations: HIFU=high intensity focused ultrasound; N=number of participants; SD= standard deviation; UAE= uterine artery embolization

Table ES-C. Final health outcomes reported in surgical studies

Arm Class	Outcome Category	Studies Reporting	Sum Baseline N	Mean followup duration	Followup Months, SD
Endometrial Ablation	Symptom status	1	96	12	0
Hysterectomy	Symptom status	4	1285	15.7	10.6
	Fibroid characteristics	1	19	6	0
	Subsequent treatment for fibroids	3	62	22	12.3
	Satisfaction with outcomes	2	614	1.5	1.4
Hysterectomy or Myomectomy	Symptom status	3	812	10.1	2.8
	Pregnancy outcomes	2	71	12	0

Arm Class	Outcome Category	Studies Reporting	Sum Baseline N	Mean followup duration	Followup Months, SD
	Fibroid characteristics	1	20	12	0
	Subsequent treatment for fibroids	1	128	6	0
	Satisfaction with outcomes	2	109	9	3
Myomectomy	Symptom status	4	1573	20.8	8.6
	Pregnancy outcomes	3	2723	22.8	11.9
	Sexual function	1	416	6	0
	Fibroid recurrence	5	349	16.9	15.4
	Subsequent treatment for fibroids	3	417	10	4.5
	Satisfaction with outcomes	1	170	0	0

Abbreviations: N=number of participants; SD= standard deviation

Expectant Management

We did not identify any studies intentionally designed to determine outcomes of no intervention also called expectant management or watchful waiting. However, 14 small RCTs designed to evaluate interventions compared a treatment to no intervention, typically trials that compared a medication with placebo. One of these trials one was of good quality, five were fair, and eight were poor quality. The evidence, based on an average followup time of 7 months (range: 3 to 12 months), suggests the size of fibroids does not meaningfully change over short timespans. Neither of the two studies with women who were postmenopausal and followed for a full year detected an increase in total volume of fibroids.

Likewise, bleeding characteristics, such as days of bleeding and severity of bleeding as measured by hemoglobin, heaviness of periods, severity of heavy bleeding episodes, did not change meaningfully during followup for those without active management. The proportion of the 457 women enrolled in these trials who presented specifically with problem bleeding, as opposed to other fibroid-related symptoms, is not known. However, the data suggests that women with fibroids should not expect that bleeding patterns will worsen over the near term.

Pharmaceutical Management

We identified 40 studies assessing effectiveness of pharmaceutical treatment for uterine fibroids. Nine studies had placebo or no treatment comparison groups. Approximately one third were industry sponsored. The longest duration of followup after the end of treatment was 36 months in one study. Women included in the studies were predominately premenopausal (36 studies). Four studies evaluated therapies in postmenopausal women. We assessed two as good quality, 12 as fair quality, and 26 as poor quality for effectiveness outcomes.

GnRH agonists

Sixteen RCTs (eighteen publications) addressed GnRH agonists, which included seven with addition of a second agent to a GnRH agonist. The studies were small with an average of 59 (1,065 total) participants and followup was typically limited to the immediate end of treatment. Only six studies followed women post-treatment, for three to six months. GnRH agonists reduce the size of fibroids, with reductions in volume of fibroids documented between 64 and 175 cm^3 and reductions in the total volume of the uterus between 131 and 610 cm^3.

Five studies reported absence of bleeding, three noting statistical significance for clinically important reduction from baseline. One study reported reduction in days of bleeding (significance not reported), and four reported improvement in hemoglobin levels (significant in 3). No study reported an increase in bleeding or worsening in hemoglobin or hematocrit. Individual women in several studies discontinued treatment because bleeding became more irregular or did not decrease.

Pain symptoms improved by GnRH treatment included pelvic pressure, pelvic and abdominal pain, and dysmenorrhea. Other studies reported similar improvements but without statistical comparisons of baseline to followup. Studies of leuprolide (with and without add-back therapy) also reported significant improvement in fibroid related symptoms (menorrhagia, pelvic pressure, pelvic pain, urinary frequency, and constipation). Mood and quality of life were also improved by treatment. Harms associated with GnRH included onset of menopausal symptoms, unfavorable changes in lipid profile, declines in cognitive function and memory, and bone loss.

Progestins and Progestin Antagonists (Mifepristone)

Seven studies (eight publications) provided data about outcomes of mifepristone treatment. Average length of time for off-medication followup was 11 months with the longest untreated followup being 12 and 18 months. All studies observed a decrease in the size of fibroids at the completion of the period of active treatment. The magnitude of change in size of the largest fibroid ranged from a decrease of 37 cm^3 to 95 cm^3, with an average of 71 cm^3 among the 575 women studied. Total uterine volume also decreased across women receiving mifepristone. Durability of effects is not clear given loss to followup.

All studies that assessed bleeding reported treatment reduced heaviness of bleeding. Two placebo comparisons found active drug superior. Women were more or equally likely to have decreased bleeding or absent menses on the lower doses compared to the higher doses. Each of six RCTs that evaluated pelvic pain before and at conclusion of treatment noted substantial improvements (present in 68%-100% at baseline compared with 9%-28% after 3 months of treatment); findings were similar at the conclusion of 6 to 9 months of treatment and maintained post-treatment in roughly 60 percent to 90 percent of women in three RCTs with longer term followup. Studies also reported significant improvements in quality of life measures. Harms included spotting, elevations in liver function enzymes, and endometrial hyperplasia.

Ulipristal Acetate

Four RCTs addressed ulipristal. All four studies found ulipristal effective for reducing the size of individual fibroids and the overall fibroid burden as measured by total fibroid and uterine volume. Ulipristal, as intended, resulted in absent menses for the majority of women during treatment (range 62 to 100%), and the majority reported improved bleeding and improved or stable hematocrit or hemoglobin. All ulipristal doses compared to placebo resulted in improved fibroid-related quality of life. Among 277 biopsies, three cases of confirmed hyperplasia (one with atypia) were reported. Two studies[12,13] also reported modest elevations of liver function enzymes during treatment, and no studies reported adrenal blockade.

Estrogen Receptor Modulators and Antagonists

Three studies investigated raloxifene in comparison to placebo, and a single study evaluated tamoxifen, which acts as an anti-estrogen within breast tissue and as an estrogen ligand in the endometrium. Fibroid size decreased in two studies of raloxifene, was not statistically different

at end of followup in one study, and was not reported in the single trial of tamoxifen. In raloxifene studies with premenopausal women, neither bleeding pattern nor hemoglobin levels were improved compared to placebo. Among postmenopausal women, the percent of treatment cycles without bleeding was similar and the number of episodes of spotting and severity of bleeding were similar among women in the treated and control group. Tamoxifen use in premenopausal women also did not influence length or severity of bleeding compared to placebo. Women receiving tamoxifen had less pain after four months of treatment compared with placebo. No studies focused on improvement in other symptoms or reported quality of life. No studies reported serious adverse effects.

Procedural Management

We identified 25 studies assessing procedural treatment for uterine fibroids. Most compared similar procedures, two compared to a different procedure, and nine were compared to surgery or medications. The longest duration of followup after the end of treatment was five years in two studies. Women included in the studies were predominately premenopausal. We assessed five as good quality, eight as fair quality, and twelve as poor quality for effectiveness outcomes.

Uterine Artery Embolization (UAE) and Occlusion

We identified 19 studies that randomized women to UAE, uterine artery coagulation, or uterine artery occlusion. We assessed five as good quality, eight as fair quality, and six as poor quality for effectiveness outcomes. Fibroid and uterine volume decreased significantly and consistently following UAE (up to 12 months post-procedure) regardless of the embolization agent or size of particles used to occlude the fibroid arteries. Longer-term followup reports from the EMMY trial confirmed that fibroid and uterine volume reductions persisted up to 5 years after UAE; however, 28 percent (23/81) of women underwent subsequent hysterectomy. Subsequent treatment was reported in seven trials with length of followup ranging from 6 to 60 months. Hysterectomy was the most frequent intervention (17.5%) followed by myomectomy (8.8%), repeat embolization (6.3%), IUD (8%), medication (6.7%), and endometrial ablation (1.2%).

Bleeding effects were consistent, with declines in bleeding or bleeding-related measures reported in most RCTs. One study of PVA versus tris-acryl microsphere reported 9 of 60 women had followup surgery for recurrent heavy menorrhagia 1 to 6 months after initial treatment.[14] Pain improved in most women in studies reporting this outcome (2 of 2). Only eight studies of UAE reported changes in quality of life, which consistently improved post-procedure with durability in the two studies with longer-term followup. Treatment satisfaction was high in seven studies reporting this outcome.

No women receiving UAE required transfusion; major complication rates during and following UAE ranged from 1.2 to 6.9 percent periprocedurally, up to about 5 percent at two years. The rate of major complications was high in two studies that reported long-term followup (21% at 5 years in the REST trial and 16.8% at 32 months in a second study) in part because they considered a subsequent procedure a complication.

Magnetic Resonance Imaging (MRI) Guided Focused Ultrasound (MRgFUS)

Five RCTs assessed high intensity focused ultrasound (HIFU), but no studies used MRI guidance. All were rated as poor quality primarily due to lack of masking of participants and assessors. In three RCTs reporting effects on fibroid size, the magnitude of fibroid volume

reduction was greater at 12 months after ultrasound destruction than at 1 month post-treatment. Studies did not report on bleeding, pain, or pregnancy outcomes. Few studies addressed quality of life, though one reported improvements in sexual function. One study reported no transfusions among 48 participants. No study reported major complications.

Fibroid Ablation

Two RCTs, both assessed as poor quality, addressed either radiofrequency or volumetric thermal ablation of fibroids. Both studies reported the technique was successful in treating 85 percent of more of the fibroid volume. Studies did not report bleeding or pain outcomes and noted no major complications.

Surgical Management

We identified 36 studies with at least one arm that assessed surgical intervention (endometrial ablation, myomectomy, or hysterectomy) for uterine fibroids. One compared myomectomy to hysterectomy, the remainder evaluated outcomes compared with women treated by UAE, other methods of vascular occlusion, HIFU, or medication. The longest duration of followup after the end of treatment was 60 months in one study. Women included in the studies were predominately premenopausal. We assessed nine as good quality, eleven as fair quality, and sixteen as poor quality for effectiveness outcomes.

Endometrial Ablation

One fair quality study addressed endometrial ablation and reported significant decreases in bleeding after both roller ball ablation and thermal balloon ablation, with similar rates of re-intervention (9%) in both groups. More women in the roller ball group had complications, but more than a third of women receiving each intervention noted dissatisfaction with ablation results.

Myomectomy

Thirteen RCTs reported health outcomes after myomectomy and six additional studies provided harms outcomes. We assessed four as good quality, six as fair quality, and nine as poor quality for effectiveness outcomes. Studies did not report changes in fibroid characteristics or bleeding; one study described change in undefined symptoms (relief in 51/88 women). Two studies noted fibroid recurrence in 5 to 27 percent of participants over 6 months to 3 years followup. Laparoscopic myomectomy was associated with faster return to usual activity than comparator surgeries in three studies and with improved quality of life compared with hysterectomy in one study. Laparoscopic myomectomy was also associated with better fertility and pregnancy outcomes than other myomectomy techniques in one study, but outcomes were mixed or comparable in other RCTs. Conversion from myomectomy to another procedure ranged from 0 to 17 percent in eight studies (n=658). Harms associated with myomectomy included transfusion, pelvic organ injury, readmission or reintervention. Harms generally did not differ among techniques.

Hysterectomy

We identified 14 RCTs assessing hysterectomy in women with uterine fibroids. Seven reported harms only (i.e., did not report final health outcomes for effectiveness). Assessment duration (where clearly reported) in comparative studies ranged from 15 days to 24 months. We

assessed five as good quality, three as fair quality, and six as poor quality for effectiveness outcomes. Among studies reporting health outcomes, one noted a decrease in hemoglobin postoperatively, and two others reported increases in hemoglobin levels at 24 months after surgery. Pain symptoms typically improved in three RCTs reporting outcomes of fibroid-related pain. Time to return to usual activity after hysterectomy averaged 30 to 40 days in three studies reporting. One study reported faster recovery (mean 22 days) after laparoscopic hysterectomy. Women reported good or very good satisfaction postoperatively, though one study reported worsened physical health compared with baseline measures at 5-year followup.

The rate of transfusion following hysterectomy ranged from zero to 20 percent in 890 women from 11 studies. An event of organ perforation occurred in one study, and overall risk across studies cannot be calculated since bowel and bladder injury were not uniformly documented or reported across studies.

Direct Comparisons of Interventions

In total 18 studies compared the effectiveness of different categories of interventions. We identified five studies designed to compare outcomes across different categories of drugs (e.g., GnRH vs. hormone replacement). These studies were small and inadequately powered for providing definitive evidence. Two studies compared high intensity focused ultrasound (HIFU) frequency ultrasound ablation methods to other interventions, with greater tumor destruction after radiofrequency ablation compared with HIFU, and comparable sexual function after HIFU or myomectomy, but faster recovery in the HIFU groups.

Other direct comparisons of procedures included comparisons of UAE to myomectomy or hysterectomy. Technical success and quality of life were similar between UAE and myomectomy but reintervention rates were higher with UAE. Pregnancy outcomes were superior in women undergoing myomectomy. Symptom relief and quality of life outcomes were generally similar between UAE and hysterectomy, with faster recovery associated with UAE. Subsequent treatment rates were higher in the UAE group than in the hysterectomy group at each time point in followup; however, the majority of women randomly assigned to have UAE avoided hysterectomy for the duration of followup, which included five years of surveillance in the largest study. Less than one in three women with UAE required additional treatment.

Analysis of Subsequent Treatment Following Initial Treatment for Uterine Fibroids

From data reported in 48 studies, we estimated the probabilities of receiving additional treatment for fibroids after randomization to a given initial treatment. Rates of subsequent intervention ranged from zero to 40 percent for women in their 30s, 40s, and 50s. Overall, fewer than half of women had another intervention within 24 months. Rates of subsequent intervention were lowest for initial medical management and higher following myomectomy or UAE. UAE was most often followed by myomectomy among those in their 30s. Younger women who initially had myomectomy were most likely to have repeat myomectomies over the two years of followup. After medical treatment, very few women in any age group had subsequent treatment within two years.

KQ 2: Influence of Patient/Fibroid Characteristics on Effectiveness

Among 90 randomized clinical trials of interventions, none were explicitly designed to address whether intervention effectiveness varied by patient or fibroid characteristics. Six studies

provided some information about influence of characteristics on outcomes within or across arms (2 of medications, 2 comparing UAE and surgery, one of myomectomy vs. no treatment, and one assessing the effects of baseline characteristics on outcomes among women who received high intensity focused ultrasound or radio frequency ablation). None were statistically powered to examine effect modification by characteristics within arms to provide information that could be used to guide care based on individual or fibroid characteristics.

KQ 3: Risk of Sarcoma when Mass is Believed to be a Fibroid

We replicated and updated the search from a recently published meta-analysis of prevalence of leiomyosarcoma among women treated for benign uterine fibroids.[9] We added 14 cohort studies published since the conduct of the prior meta-analysis. We fit a binomial random effects model to update the estimate of prevalence of identifying a leiomyosarcoma at the time of surgery for presumed fibroids. Estimate prevalence is 0.07 percent (95% credible interval: 0.03 to 0.10), or in other words, an unexpected sarcoma will be identified in 3 to 10 surgeries of 10,000 surgeries performed for fibroids. Estimates from prospective studies were five in 10,000, whereas retrospective were eight per 10,000, though lack of precision means they are not credibly different.

KQ 4: Influence of Morcellation and Patient/Fibroid Characteristics on Risk of Dissemination

Survival time for women with uterine sarcoma for whom power morcellation was used, compared to survival of women for whom sharp morcellation (with a scalpel) was used to assist removal of the surgical specimen is similar. Even when the uterus was removed intact (because of known sarcoma or surgeon's preference), survival times were similar to both forms of morcellation. This analysis suggests the fact or method of morcellation is not strongly associated with the overall lethality of this aggressive form of cancer.

Discussion

KQ 1. Effectiveness of Treatments for Fibroids

Expectant Management

Our findings of minimal change over followup periods of a year or less are compatible with a prior review that included observational cohorts.[11] The number of women in the literature followed without intervention is small and the total picture provided is insufficient to project what the course of watchful waiting may be for an individual woman. Because none of these studies were designed to evaluate expectant management, the overall quality of the research is poor to inform choice of expectant management over other options and strength of the evidence is low.

Pharmaceutical Management

GnRH Agonists

GnRH agonists reduce the size of fibroids and the overall size of the uterus (moderate strength of evidence). Add-back medication such as estrogen, progestin, or tibolone, is frequently

given in conjunction with GnRH agonists to alleviate the undesirable side effects of anti-estrogens. The evidence suggests improvements in bleeding symptoms (e.g., anemia) with and without add-back therapy. Fibroid related pain and other symptoms improve with single agent treatment and with add-back treatment. Add-back medication relieves associated menopausal symptoms and can ameliorate bone loss and lipid changes. One trial examined outcomes of treatment after more than 24 months and found that effects can be maintained over two years. Extended follow-up of women after they discontinue GnRH agonists is not available, thus information about long-term effectiveness and potential harms of treatment is lacking.

Mifepristone

Moderate evidence supports that mifepristone reduces size of fibroids and overall uterine volume. Heaviness of bleeding is reduced during treatment and measures of anemia also improve. Evidence is insufficient to contribute to dose selection between higher and lower doses. Higher doses are inconsistently associated with greater reduction in size and faster resolution of symptoms but may also come with more nuisance bleeding. Since the medication is an oral daily agent, dose changes can be easily accomplished. Weak evidence suggests fibroids do resume growth after treatment; however, the majority of women can achieve symptomatic relief for a year or more after cessation of active treatment. Few participants in these trials pursued other treatment during medical management or in the time after concluding active treatment suggesting, along with moderate strength of evidence for improvement in quality of life, that treatment with mifepristone can provide sufficient management of fibroid related symptoms.

Ulipristal

Moderate evidence supports that ulipristal reduces size of fibroids. Heaviness of bleeding is reduced with most women reporting absence of menses during treatment and measures of anemia stabilized or improved. Data were not available to gauge whether fibroids resume growth after treatment. Extended followup of participants after treatment cessation is needed. More information is needed to contribute to dose selection between higher and lower doses. Use of a progestin for 10 days to prompt onset of menses shortened the time between treatment cycles in a single study. Along with moderate strength of evidence for improvement in quality of life, this suggests treatment with ulipristal can be acceptable and sufficient for management of fibroid related symptoms.

Estrogen Receptor Agents

These agents were variably related to no or small decreases in fibroid size without improvement in bleeding. Some authors endorsed a focus on these medications because they are used for other indications and will be given to women with fibroids. These studies provide low strength of evidence that raloxifene and tamoxifen will not cause significant growth of existing fibroid or exacerbate bleeding if they are needed to treat women with fibroids for other conditions such as extended organ specific hormone suppression after breast cancer treatment.

Procedural Management

We include 25 studies addressing uterine artery embolization, uterine artery occlusion, HIFU, and fibroid ablation.

Uterine Artery Occlusion

Compared to myomectomy, length of stay and transfusions were lower after UAE, however, re-intervention rates were higher for women treated with UAE than for those treated by myomectomy. Reproductive outcomes were reported to be superior after myomectomy compared with UAE among a subgroup of participants from a small study. Quality of life, symptom relief, and fibroid recurrence were similar between UAE and myomectomy groups. Incidence of major complications was also similar between groups.

Compared with hysterectomy, UAE was associated with a shorter hospital stay. Re-intervention rates, bleeding symptoms, and need for subsequent treatment were higher among patients treated with UAE versus hysterectomy. Changes in quality of life, sexual function, pain, and satisfaction were similar between UAE and hysterectomy groups. Although the incidence of major complications was not different, surgical removal of the uterus was associated with more bladder problems, and an increased need for blood transfusion.

HIFU and MRgFUS

Studies of HIFU reported few outcomes. These studies reported predominantly intra- and postprocedural outcomes, specifically technical success, and safety of the technique. Fibroid and uterine size was reduced in studies that measured this outcome but strength of evidence is low because of short followup and poor quality of overall study design. With the exception of one study that assessed sexual function, publications did not assess symptoms or long-term outcomes. Evidence related to patient reported outcomes is insufficient.

Fibroid Ablation

Only two small studies evaluated thermal or radiofrequency ablation techniques for fibroid removal. These studies on reported technical success and safety of the technique, but did not address symptoms or long term outcomes. These procedures are not done widely in practice and strength of the evidence is insufficient to inform care.

Surgical Management

Most surgical studies did not follow patients beyond the postoperative period. Therefore, many studies did not report patient-specific, or symptom related outcomes such as change in fibroid related pain or fibroid-related bleeding. Many of the studies with surgical or procedural interventions reported intermediate outcomes only, such as technical success, hospital length of stay, or estimates of blood loss related to the surgery (e.g., postoperative hemoglobin, intra or postoperative transfusion rate).

Endometrial Ablation

A single fair quality study found endometrial ablation by balloon or roller ball methods improved bleeding as measured by self-report and clinical lab values. After 12 months, more than one-third of patients in each group were not satisfied with the outcome. Evidence is insufficient to choose among methods, and some women will seek subsequent intervention.

Myomectomy

Evidence is moderate that myomectomy is associate with improved fibroid characteristics (volume/size) and quality of life. Myomectomy is an option for women desiring future fertility. Studies reported fibroid recurrence assessed by ultrasonography up to 3 years after treatment in 30 among 286 women available for followup. Women who have laparoscopic procedures have

shorter recovery time than those who have abdominal incisions. Of note, the evidence is insufficient to determine if myomectomy statistically meaningfully improves bleeding patterns or anemia.

Hysterectomy

Hysterectomy removes all fibroids and resolves bleeding but with distinctive trade-offs including making pregnancy impossible and the long-term sequelae of hysterectomy for any reason such as increased risk of urinary incontinence. If a hysterectomy is desired, choice of route of surgery is a concern. Overall, patient satisfaction and recovery time following hysterectomy was better for women who received a vaginal hysterectomy compared to total abdominal hysterectomy. Harms, including the need for blood transfusion and organ perforation were similar for all types of hysterectomy.

Summary of Findings from Studies for KQ 1

We include a summary table to present key findings and the overall strength of evidence assessment for three final health outcomes, fibroid volume, fibroid-related bleeding, and quality of life reported most frequently in the publications of eligible studies for KQ 1 (Table ES-D). For the complete assessment of strength of evidence, including risk of bias, study limitations, reporting bias, precision, consistency and directness of results, see the summaries presented in the Full Report.

Table ES-D. Strength of evidence and summary of findings for intervention effects on fibroid volume, fibroid-related bleeding, and quality of life

Intervention Category	Key Findings
Expectant Management	Low SOE for any clinically significant change in fibroid volume, bleeding symptoms, or improvements in quality of life during the short term with expectant management.
GnRH agonist	Moderate SOE for reduction in fibroid size and uterine volume and improvement in fibroid-related bleeding symptoms during treatment with GnRH agonists. Insufficient SOE for GnRH agonist effects on quality of life.
Mifepristone	Moderate SOE that mifepristone reduces the size of uterine fibroids. Effects on fibroid volume did not persist after treatment stopped. Moderate SOE for reduction in bleeding and improvement in uterine fibroid related quality of life.
Ulipristal	Moderate SOE that ulipristal reduced the size of uterine fibroids. Fibroid volume improved consistently in ulipristal (doses between 5 and 20 mg) compared with placebo. Moderate SOE for improvements in bleeding, including cessation of menses and higher or stable hemoglobin levels and moderate SOE for improvement in fibroid related quality of life.
LNG-IUD	Insufficient evidence for IUD effects on fibroid size, changes in bleeding outcomes, or quality of life outcomes.
Estrogen receptor agents	Low SOE for fibroid size reduction following three months of raloxifene or tamoxifen treatment. Low SOE for no change in bleeding pattern and no change in hemoglobin levels in premenopausal women treated with raloxifene or tamoxifen.
Uterine artery occlusion	High SOE for significant reductions in fibroid volume following UAE. Data from two long-term studies reported reductions persisting up to 5 years. Low SOE for improvement in bleeding symptoms. Moderate SOE for improved quality of life (improved physical well-being) following uterine artery occlusion of fibroids.
HIFU	Low SOE that fibroid volume decreased following HIFU. Insufficient SOE for HIFU effects on bleeding symptoms or quality of life.
Fibroid Ablation	Evidence is insufficient for fibroid ablation effects on fibroid volume, bleeding outcomes or quality of life.
Endometrial ablation	Insufficient SOE for changes in bleeding symptoms or quality of life following endometrial

Intervention Category	Key Findings
	ablation
Myomectomy	Moderate SOE that fibroid related quality of life improved following myomectomy.
Hysterectomy	Low SOE that women reported improved quality of life following hysterectomy.

Abbreviations: GnRH= gonadotropin releasing hormone; HIFU= high intensity focused ultrasound; LNG-IUD= levonorgestrel intrauterine device; NA= not applicable; SOE=Strength of Evidence

Comparative Effectiveness

Studies comparing different categories of intervention were rare. Most were single studies of the specific comparison investigated. Because of quality and size of these single comparison studies, evidence is insufficient to guide care. Among five studies comparing across category of drugs, no medical management strategy was shown to be superior. Vascular occlusion of the uterine arteries was comparable to myomectomy for key outcomes, with the exceptions that pregnancy outcomes are less favorable after UAE and women who have UAE are more likely to need subsequent intervention for fibroids. This is based on two fair quality studies, providing low strength of evidence. In three studies comparing UAE to hysterectomy and another comparing UAE to patient choice of myomectomy or hysterectomy symptom relief and quality of life was similar across groups. Comparisons for fibroid size and bleeding are not possible in the sense that after removal of the uterus the fibroids are removed and bleeding ceases. Comparisons of sexual function following surgery or procedural intervention were reported rarely. Fewer harms were associated with UAE. Under half of patients had a subsequent intervention after UAE, out to five years of followup. This amounts to low to moderate evidence that UAE can achieve the outcomes desired by patients, while leaving options open for subsequent treatment as needed or desired.

Subsequent Intervention

For each of these intervention (uterine artery embolization, myomectomy, and medical management) and the subsequent treatment possibilities, the information is intriguing but insufficient based both on the overall quality of trials and small number of women followed up over time. It is likely that much fewer than half of women will choose subsequent treatment in the near-term. However, we can also speculate that the priorities which led women to participate in the initial trial reflected the intensity of treatments they were most interested in pursuing so it is not surprising surgeries were most followed by other procedures promptly (within 6 months) by those were not satisfied with initial results while those who enrolled in medication trials were less likely to pursue more aggressive options. Because of the limited roster of studies that followed women for 6, 12, or 24 months, this analysis does not substitute for study of treatment trajectories in which all initial treatments can be followed by all possible combinations of next treatments.

KQ 2. Treatment effect modifiers: patient and fibroid characteristics

Overall, there is insufficient evidence for women to choose one intervention over another based on her individual characteristics or the characteristics of her fibroids. Too few studies were adequately powered to determine within arms if one subgroup or another has superior outcomes within a treatment. Such information is required as a first step towards using individual characteristics to inform treatment choice.

KQ 3. Morcellation of fibroids and risk of uterine sarcoma dissemination

The literature investigating the prevalence of sarcoma in presumed fibroids has grown rapidly and this continues to enhance the precision of risk estimates. Overall 3 to 10 women in every 10,000 who have surgery for fibroids may be found to have a sarcoma. Actual rates of dissemination that result in a fragment becoming a cancer implant leading to disseminated disease are more difficult to estimate. Nonetheless, the risk of dissemination would not be expected to be higher than 0.10 percent for a population of women having fibroids surgery because it cannot exceed the risk that a tumor is present.

KQ 4. Patient or fibroid characteristics and risk of uterine sarcoma dissemination following morcellation

At this time, definitive evidence that power morcellation is associated with poor long-term outcomes when unsuspected sarcoma is present is limited. Evidence from observational studies is insufficient to conclude that power morcellation is a predominant determinant of disease state and survival. This literature did not identify characteristics of women or their fibroids, beyond increasing age, to inform determination of who might be good or bad candidate for morcellation (sharp or power). Data from the available literature suggest comparable lethality of sarcomas across surgical methods. We did not find evidence to suggest that abandonment of morcellation will improve patient outcomes. Subjecting all women to open procedures, especially for myomectomy when some disruption of tissue planes is inevitable regardless of surgical approach, is not supported by this review. The uncertainty of uterine sarcoma dissemination following morcellation and the potential risks associated with open procedures call for explorations of ethical and shared-decision making topics to offer coherent care recommendations that support patients' and surgeons' autonomy.

Applicability

Overall, our findings are applicable to the general population of women seeking treatment for uterine fibroids. We did not identify studies designed to evaluate expectant management, but information from over 1,000 women from 14 study arms who received placebo or no intervention suggest little change in fibroid size or bleeding outcomes during relatively the short duration of follow-up (6 months or less). The comparators in the majority of these studies were medications available in the United States with the exception of single studies of tibolone[15] and asoprisnil.[16] Medical management of fibroids was assessed in over 2,200 predominately premenopausal women in 40 studies (13 industry sponsored; 11 conducted in the United States). These studies were of shorter duration and typically did not follow-up after end of treatment.

Procedures, including uterine artery embolization, high intensity focused and magnetic resonance-guided focused ultrasound and ablation were evaluated in 25 studies including almost 2000 women. Two long-term studies of embolization compared to surgery provided information on patient satisfaction, quality of life, and need for followup interventions and are highly applicable to decision-making. Limited information on fertility and pregnancy outcomes following uterine sparing procedures is available.

Surgical studies evaluated hysterectomy, myomectomy, and ablation in over 3,000 women. Although none of these studies were conducted in the United States, the surgical techniques described here are comparable. The comparators are also widely available to women in the

United States. The majority of surgical studies did not include any long-term followup so outcomes of patient satisfaction and quality of life including sexual function are not known.

There was insufficient data from a small number of studies to evaluate patient or fibroid characteristics that influence effectiveness outcomes (KQ 2). Although data was lacking for some interventions (ablation was evaluated in only two small studies, IUDs in one), the treatments described for uterine fibroids in this review should be generally applicable to women in the United States seeking one of the many treatment choices currently available for this condition.

Limitations of the Systematic Review Process

Methodologic choices constrain the findings of this report. We chose to focus on publications in the English-language literature, to restrict to randomized clinical trials, and to review only those studies that included at least one intervention that is available in the United States. Similar reviews have documented in the past that language restrictions do not increase risk of omitting high quality trials. This is especially true for the topic of fibroids because the fibroid research community is small. Our technical expert panel and authors are familiar with prior and ongoing work and helped assure relevant studies have not been overlooked. Restricting to trials allowed us to sharply focus on proof of effectiveness. Because all individuals whose outcomes were assessed in these studies were randomly assigned to the intervention received, provider and patient biases in intervention choice are reduced and risk of confounding, that is difficult to fully assess or adjust for in cohorts, is minimized. Reduced risk of bias in assignment in trials allows aggregation and summary of the findings by study arm, as we have done in this report.

We have used meta-analysis techniques to help focus on where there is precision and on what knowledge remains elusive. Our analysis of subsequent intervention after a first intervention could be biased by the types of studies that reported this data. For meta-estimates related to morcellation risk, available evidence based on pathology specimens for estimating presence of sarcoma in a mass believed to be a fibroid is accruing and will likely continue through and past the production of this report. Our estimates and that of Pritts and colleagues[9] find that the estimates are lower in data from more contemporary prospective cohorts of women having surgery. This suggests some inaccuracies in retrospectively collected data even when pathology specimen banks are used to index a full population of surgical patients. This risk of inaccuracy is especially true in understanding and estimating the potential that morcellation method influences survival when a woman is found to have a sarcoma that was believed to be a fibroid.

Focusing on interventions available in the United States, and excluding those that cannot be obtained here could neglect a promising intervention but does restrict the report to data that is of immediate value to women and their care providers who must make decisions among available options. We have included interventions that are not widely available in the United States such as high frequency ultrasound ablation and operative thermal ablation, so in the strictest sense of applicability, some women live in locations, or have access to a limited group of providers or face limitations of insurance coverage that may restrict the availability of some options.

Limitations of the Evidence Base

While the literature about the effectiveness of uterine fibroids treatment has grown since 2007, significant gaps in knowledge persist. The 90 studies with 97 unique intervention arms enrolled only 8,331 women. Individual studies were often small and powered to address a single continuous outcome such as hematocrit or score on a quality of life scale.

Our causal framework was created to reflect the outcomes that matter to women when making decisions. The available literature has substantial gaps in collecting this information as indicated by the number of studies that addressed each of our eight primary outcomes. Fibroid characteristics and symptom status were the most frequently reported outcomes, addressed in 57 percent of the studies, though assessment techniques and measures varied. Other key outcomes including quality of life and satisfaction with outcomes (9%), sexual function (11%), and future reproductive outcomes (8%) were addressed in only a handful of studies. Detailed descriptions of subsequent treatment were reported in 19 (21%) of the included trials.

Little continuity exists in approaches to measuring outcomes and use of unvalidated measures is common. When data is combined across studies for a particular intervention, risk of serious rare harms cannot be fully assessed. In many instances ability to synthesize evidence across studies is absent, weak because of biased collection methods (e.g. assessors not blind to intervention), or difficult to aggregate across studies because of use of different metrics.

Paucity of "similar" articles (populations, settings, patient characteristics, and outcomes measured) also precludes efforts to pool data about characteristics of the study populations as they contribute to predicting outcomes. No studies were appropriately powered to understand whether specific groups of patients, such as those closer to menopause or with a specific symptom pattern have outcomes that are modified by those characteristics. Lastly, the lack of direct comparisons limits the information this can provide to help a woman or her care provider make an evidence-driven selection among choices in the context of the patient's priorities.

Research Recommendations

Key components of study design, analysis, and reporting remain the leading weaknesses of the literature for each topic addressed in this review. Overall, the literature identified is limited by the following gaps and problems discussed in detail in the full report. Future research should aim to remediate these concerns:

- Ability to assess internal and external validity
- Study populations of adequate size for assessing key outcomes
- Use of standard nomenclature and validated measures
- Analysis methods matched to the outcomes of interest
- Direct comparisons of treatment options

A range of content priorities also need to be addressed. These include the burden of disease and societal costs from loss of ability to function well in the usual family or occupational roles. Transitions associated with appearance of uterine fibroids, growth patterns, and influences on growth (e.g., concurrent medical conditions like diabetes, use of medications like hormonal contraception, influence of lactation and duration) are high-priority topics, as are predictors of symptom development and resolution. Variation in care-seeking behaviors, differences in severity at presentation, and health and quality-of-life outcomes are other matters that investigators should attempt to address. This literature cannot currently address from trials whether disparities between white and black women in the age at appearance of fibroids and in the number and size of fibroids also foreshadows different treatment outcomes and durability of results.

Current practice suggests that women without symptoms may forego intervention because of the general belief that care should be aimed at improving symptoms or addressing a specific clinical concern such as difficulty conceiving or recurrent pregnancy loss. Although foregoing intervention can be wise in the absence of data that the intervention will prevent future

difficulties, we emphasize that no data yet support expectant management as a “safe” choice; neither do any data indicate whether use of therapeutics short of surgery might forestall or prevent future changes in fibroids or appearance of symptoms. The concept of preventive strategies is appealing. However, as long as the etiology of fibroids remains unclear, medical treatment choices are few, and preliminary trials are not assessing lifestyle interventions, the prospect for dietary management, exercise, hormonal management, or other prevention trials is slim.

The clinical research agenda will likely depend on new translational research and large-scale epidemiology studies that are yet to be done. Much remains to be learned that will require large-scale prospective observational studies of sufficient size and rigor to support time-to-event analysis of outcomes, such as that being conducted in the COMPARE Uterine Fibroids 10,000 woman cohort supported by AHRQ and PCORI. These studies may afford greater power to examine effect modification and to determine trajectories of care over a reproductive lifespan for women with fibroids. Research effort must be focused on documenting first the course and consequences of uterine fibroids using optimal imaging strategies, then the modifiers of that course and of the effectiveness of treatment, so that we can offer women an accurate account of the likely outcome of expectant management based on their individual status.

Conclusions

Direct comparisons among treatment options remain sparse. No studies have explicitly evaluated expectant management, which is a crucial missing piece of the evidence about whether symptoms relapse and remit. The literature must come to include uniformly longer followup to determine whether women’s objectives for treatment were met by the intervention received. Few women have only one concern driving their desire for intervention, yet remarkably many trials are directed at evaluating a single outcome.

Across management options, we must note that lack of evidence is not equivalent to evidence of no benefit or of harm. Some of these interventions are effective in some patients but evidence to inform probability or risk or benefit based on patient characteristics is lacking. Uncontrolled studies are not a substitute since they are notably biased for overestimating the degree of benefit subsequently reported in randomized trials. Indeed, not uncommonly, trials negate the findings of what in this case is largely retrospective and case series research. The current state of the literature does not permit definitive conclusions about comparative benefit, harm, or relative costs to achieve similar results across the range of available options and lacks strength of evidence for interventions such as use of continuous birth control pill regimens, progesterone containing IUDs, and endometrial ablation that are often used in routine clinical practice. Given how common and concerning fibroids can be to women and their care providers, a redoubled emphasis on promoting high-quality fibroid research in the United States is imperative. Women deserve better information to guide their choices.

ReferencesReferences

1. Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003 Jan;188(1):100-7 PMID: 12548202

2. Wise LA, Palmer JR, Stewart EA, et al. Age-specific incidence rates for self-reported uterine leiomyomata in the Black Women's Health Study. Obstet Gynecol. 2005 Mar;105(3):563-8. doi: 10.1097/01.AOG.0000154161.03418.e3 PMID: 15738025

3. Laughlin SK, Baird DD, Savitz DA, et al. Prevalence of uterine leiomyomas in the first trimester of pregnancy: an ultrasound-screening study. Obstet Gynecol. 2009 Mar;113(3):630-5. doi: 10.1097/AOG.0b013e318197bbaf PMID: 19300327

4. Monte LM ER. Fertility of Women in the United States: June 2012. Current Population Reports. 2014:P20-575

5. Myers ER, Barber MD, Gustilo-Ashby T, et al. Management of uterine leiomyomata: what do we really know? Obstet Gynecol. 2002 Jul;100(1):8-17 PMID: 12100798

6. Wegienka G, Baird DD, Hertz-Picciotto I, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003 Mar;101(3):431-7 PMID: 12636944

7. Cardozo ER, Clark AD, Banks NK, et al. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012 Mar;206(3):211.e1-9. doi: 10.1016/j.ajog.2011.12.002 PMID: 22244472

8. Hartmann KE, Birnbaum H, Ben-Hamadi R, et al. Annual costs associated with diagnosis of uterine leiomyomata. Obstet Gynecol. 2006 Oct;108(4):930-7. doi: 10.1097/01.aog.0000234651.41000.58 PMID: 17012456

9. Pritts EA, Vanness DJ, Berek JS, et al. The prevalence of occult leiomyosarcoma at surgery for presumed uterine fibroids: a meta-analysis. Gynecol Surg. 2015;12(3):165-77. doi: 10.1007/s10397-015-0894-4 PMID: 26283890

10. Matchar DB, Myers ER, Barber MW, et al. Management of uterine fibroids. Evid Rep Technol Assess (Summ). 2001 Jan(34):1-6 PMID: 11236283

11. Viswanathan M, Hartmann K, McKoy N, et al. Management of uterine fibroids: an update of the evidence. Evid Rep Technol Assess (Full Rep). 2007 Jul(154):1-122 PMID: 18288885

12. Nieman LK, Blocker W, Nansel T, et al. Efficacy and tolerability of CDB-2914 treatment for symptomatic uterine fibroids: a randomized, double-blind, placebo-controlled, phase IIb study. Fertil Steril. 2011 Feb;95(2):767-72.e1-2. doi: 10.1016/j.fertnstert.2010.09.059 PMID: 21055739

13. Levens ED, Potlog-Nahari C, Armstrong AY, et al. CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial. Obstet Gynecol. 2008 May;111(5):1129-36. doi: 10.1097/AOG.0b013e3181705d0e PMID: 18448745

14. Yu SC, Lok I, Ho SS, et al. Comparison of clinical outcomes of tris-acryl microspheres versus polyvinyl alcohol microspheres for uterine artery embolization for leiomyomas: results of a randomized trial. J Vasc Interv Radiol. 2011 Sep;22(9):1229-35. doi: 10.1016/j.jvir.2011.05.011 PMID: 21802314

15. Gregoriou O, Vitoratos N, Papadias C, et al. Effect of tibolone on postmenopausal women with myomas. Maturitas. 1997 Jun;27(2):187-91 PMID: 9255754

16. Chwalisz K, Larsen L, Mattia-Goldberg C, et al. A randomized, controlled trial of asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata. Fertil Steril. 2007 Jun;87(6):1399-412. doi: 10.1016/j.fertnstert.2006.11.094 PMID: 17307170

Introduction

Condition

Most women will develop one or more uterine fibroids (i.e., leiomyomata), benign smooth muscle tumors of the uterus, during their reproductive lifespan.[1] In the United States, an estimated 26 million women between the ages of 15 and 50 have uterine fibroids.[1-4] More than 15 million of them will experience associated symptoms or health concerns.[5,6] A disproportionate number of black women are among those with symptoms in part due to earlier age at onset of fibroids with larger and more numerous tumors.[1-3,7,8]

The etiology of uterine fibroids is not well understood, and a variety of factors including race/ethnicity, parity, and age at menarche have been examined. Health effects range from profound bleeding and anemia, to pelvic pressure or pain, urinary frequency, abnormal bowel function, and pain with intercourse, as well as concerns about influence on fertility and pregnancy outcomes.[9]

Fibroids are prevalent and symptoms are common among women with fibroids, creating considerable personal and societal costs including diminished quality of life, disruption of usual activities and roles, lost work time associated with symptoms, and substantial healthcare expenditures. Across types of interventions, direct annual healthcare costs in the United States are projected to exceed $9.1 billion. Lost wages, productivity, and short-term disability are estimated to total more than $5 billion, perhaps as much as $17 billion, with roughly $4,624 in costs per women in the first year of diagnosis.[10,11]

Management of Uterine Fibroids

Discussion of options for management of symptomatic fibroids is among the most frequent conversations in gynecology and primary care and is the most common cause for consideration of gynecologic surgical intervention.[12,13] The nature of those discussions is also fundamentally shaped by future reproductive goals and desire to retain fertility.[14,15] This report is organized from least invasive to more invasive treatment options. We move from discussion of expectant management, also termed watchful waiting, to pharmaceutical treatment, and then to procedures and surgeries.

Presence of fibroids does not require intervention; many women with one or more fibroids have no related symptoms and can work with their care providers to monitor status. Though no medications have been specifically approved by the U.S. Food and Drug Administration (FDA) for treatment of fibroid symptoms, a range of medications is used off-label to address fibroid symptoms. Those most studied in randomized trials include prescription medications that decrease production of hormones or block their actions. However the most used in clinical practice include birth control pills and non-steroidal anti-inflammatory agents, and hormone blocking. Indeed the proportion of women with fibroids likely to be receiving medical therapy to address symptoms is higher than those receiving surgery in any given year, though perhaps not over the lifetime.[10] Similarly no intrauterine device (IUD) brand has sought a specific indication for use in women with fibroids, though clinically progesterone containing IUDs are used with the goal of reducing or eliminating uterine bleeding.

Outpatient or short-stay procedures to treat fibroids include: magnetic resonance guided focused ultrasound (MRgFUS) which has FDA approval and uses ultrasound focused through the abdominal wall to destroy fibroid tissue focally. There is no skin incision. Similar, less common

techniques include radiofrequency volumetric thermal ablation and focal destruction of fibroids in situ at the time of surgery.

Uterine artery embolization (UAE) involves placement of a catheter through a blood vessel in the groin, using techniques similar to cardiac catheterization. The blood vessels serving the uterus or specific fibroids are then blocked by introducing an embolization agent to close off the blood flow through the vessel. Similar techniques can be used to occlude uterine vessels directly at the time of open or laparoscopic surgeries.

Myomectomy is the removal of the fibroid with retention of the uterus. Hysteroscopic myomectomy involves entering the uterus through the cervix and using a resectoscope or a laser to remove or destroy submucosal fibroids, which are those inside or adjacent to the uterine cavity. Subserosal fibroids that distort the outer contour of the uterus or intramural fibroids in the wall of the uterus can be removed via an open abdominal incision or laparoscopic approach working through multiple smaller ports.

Removal of the uterus by hysterectomy provides definitive surgical treatment for women who do not wish to maintain fertility. For several decades, power morcellators have been used to facilitate hysterectomy and myomectomy via conventional and robotic laparoscopic approaches. Morcellation reduces the fibroid tissue to smaller fragments that can then be removed through minimally invasive approaches. Techniques are available to remove fragments directly through a port or to place the fragments in a flexible bag system, or create the fragments inside the bag system that can then be removed through a port. Several morcellation devices received FDA approval; all currently are included in a 2014 safety communication issued by the FDA that advises against use of laparoscopic uterine power morcellators "in the majority of women undergoing myomectomy or hysterectomy for treatment of fibroids" due to the risk of disseminating cancer in women with occult uterine sarcoma.[16]

We consider the categories of interventions described above in sequence in this report.

Scope and Key Questions

Scope

To best inform clinical decisions about care we focused on evidence from randomized trials that assessed effectiveness of contemporary interventions for women of any age with fibroids. We also sought to identify factors that might modify likelihood of favorable results or harms from treatments. We included studies evaluating medications, procedures, and surgeries for the management of uterine fibroids. We also summarize data from women who were followed within trials without active intervention. In light of recent uncertainty about the risk of cancer dissemination following morcellation of fibroids during minimally invasive procedures, this review also includes literature about morcellation and risks of leiomyosarcoma.

This review does not cover preoperative adjunctive treatments such as gonadotropin-releasing hormone (GnRH) agonists or intraoperative techniques, like use of cell savers that have established effectiveness as preoperative or adjunctive interventions to minimize blood loss or otherwise improve short-term operative outcomes. We also do not review trials comparing operative devices such laparoscopic instruments for ligation versus cautery of the uterine vessels if the trial included only intermediate outcomes. Except in the context of factors assessed at the time of imaging that may help identify risk of dissemination of sarcoma, we do not address diagnostic accuracy of imaging. We did however seek to examine conventional fibroid characteristics as assessed by imaging and how they relate to achieving desired outcomes.

Key Questions

Key Question 1. What is the comparative effectiveness (benefits and harms) of treatments for uterine fibroids, including comparisons among these interventions?

Key Question 2. Does treatment effectiveness differ by patient or fibroid characteristics (e.g., age, race/ethnicity; symptoms; vascular supply to fibroids; menopausal status; or number, size, type, location, or total volume of fibroids)?

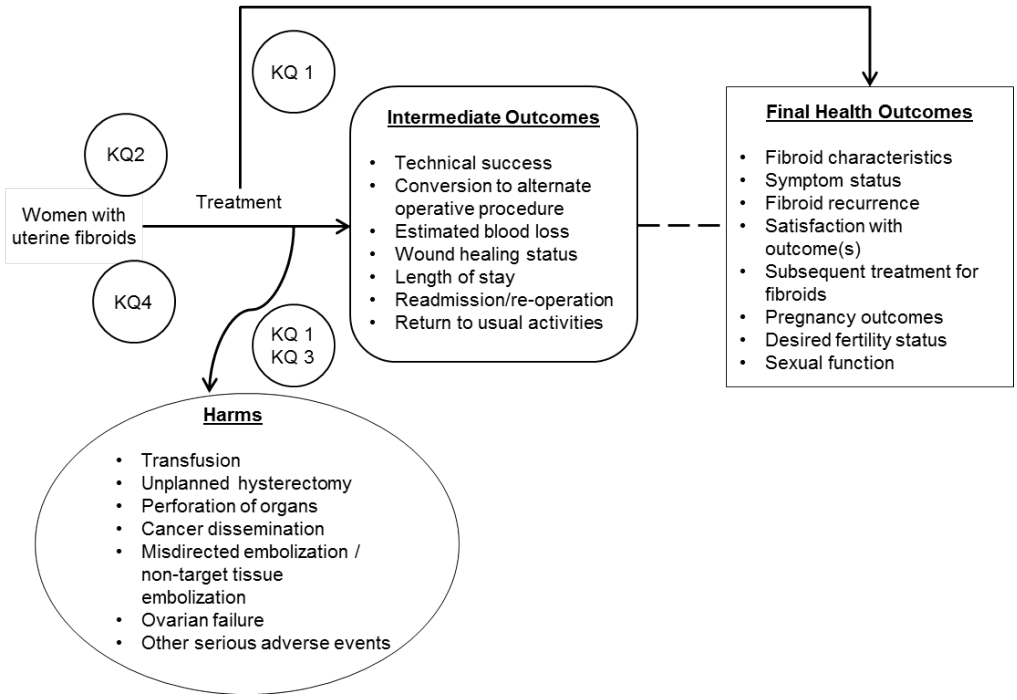
Key Question 3. What is the risk of sarcoma dissemination from morcellation of uterine fibroids at the time of myomectomy or hysterectomy?

Key Question 4. Does risk of cancer dissemination from morcellation differ by patient or fibroid characteristics (e.g., age; race/ethnicity; symptoms; menopausal status; imaging characteristics; vascular supply to fibroids; or number, size, type, location, or total volume of fibroids)?

Analytic Framework

The analytic framework provides context for our Key Questions and illustrates the population, intermediate outcomes, final health outcomes, and interest in a specific set of harms that guided the literature search and synthesis of evidence (Figure 1).

Figure 1. Analytic framework



KQ = Key Question

Methods

In this chapter, we document the procedures that the Vanderbilt Evidence-based Practice Center (EPC) used to develop this comparative effectiveness report. We first describe the development of the topic and scope of review, including formulation of key questions. We present our strategy for identifying relevant literature, our inclusion and exclusion criteria, and the process we used to abstract relevant information and synthesize evidence. We also discuss our criteria for summarizing the risk of bias for individual studies and the overall strength of the evidence for each intervention category with respect to selected high-priority outcomes. Detailed records about EPC methods are available at the Agency for Healthcare Research and Quality Effective Health Care Program website (http://www.effectivehealthcare.ahrq.gov) and key documents related to conduct of this report are included in the appendices.

Topic Refinement and Review Protocol

The EPC engaged in a public process to refine the original topic submission, draft Key Questions (KQs), and develop a systematic review protocol. A panel of 10 Key Informants provided input via teleconferences and individual communication with the team about our questions and proposed scope of the review. Key Informants represented the fields of gynecology, patient advocacy, and regulatory and industry stakeholders. The draft KQs were posted on the Agency for Healthcare Research and Quality Effective Health Care website for public review and critique for three weeks. Comments did not necessitate any significant changes to the KQs, review scope, or inclusion criteria. The EPC then recruited a panel of nine technical experts to provide high-level content and methodologic expertise throughout the review. The technical expert panel members represented the fields of gynecology, interventional radiology, reproductive endocrinology, and epidemiology. The final protocol was registered with PROSPERO (registration CRD42015025929) and posted on the Effective Health Care website (http://www.effectivehealthcare.ahrq.gov)

Finding and Selecting Studies

Published Literature

We searched MEDLINE via PubMed to identify publications (Table 1 and Table 2). The search strategies are presented in Appendix A. We limited the search to literature published after January 1985 in order to encompass modern surgical methods including the widespread introduction of laparoscopy as well as current non-surgical interventions and medications. We will conduct a literature search update during at the time of peer review of the draft report and include relevant studies with each update. We will also incorporate relevant, eligible studies identified by peer reviewers or public commenters.

Table 1. Literature search strategy: interventions for uterine fibroids

Search	Query	Results
#1	((leiomyoma[mh]) OR (fibroma[mh] AND (uterine diseases[mh] OR uterus[mh])))	17656
#2	(Uterine[tiab] AND (fibroma*[tiab] OR fibroid*[tiab] OR leiomyoma*[tiab] OR myoma*[tiab] OR fibromyoma*[tiab])) OR (submucous fibroid*[tiab] OR submucosal fibroid*[tiab] OR Intramural fibroids [tiab]) NOT medline[sb]	985
#3	#1 OR #2	18621

Search	Query	Results
#4	("Mifepristone"[Mesh] OR "ulipristal"[Supplementary Concept] OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Antifibrinolytic Agents"[Mesh] OR "Goserelin"[Mesh] OR "cetrorelix"[Supplementary Concept] OR "Selective Estrogen Receptor Modulators"[Mesh] OR "Levonorgestrel"[Mesh] OR "Nafarelin"[Mesh] OR "Triptorelin Pamoate"[Mesh] OR "Leuprolide"[Mesh])	90459
#5	(Mifepristone[tiab] OR Ulipristal acetate[tiab] OR NSAID[tiab] OR antifibrinolytic[tiab] OR Goserelin[tiab] OR cetrorelix acetate[tiab] OR Selective estrogen receptor modulators[tiab] OR SERM[tiab] OR mirena[tiab] OR lng-ius[tiab] OR levonorgestrel-releasing intrauterine system[tiab] OR management[tiab] OR leuprolide[tiab] OR triptorelin[tiab] OR nafarelin[tiab]) NOT medline[sb]	92082
#6	#4 OR #5	182541
#7	therapy[sh:noexp] OR drug therapy[mh] OR drug therapy[sh] OR complementary therapies[mh] OR cam[sb] OR Treatment outcome[mh]	4576056
#8	surgery[sh] OR surgical procedures, operative[mh] OR embolization, therapeutic[mh]	3058662
#9	(Hysterectomy[tiab] OR myomectomy[tiab] OR hysteroscopy[tiab] OR emboliz*[tiab] OR ablation[tiab] OR magnetic resonance guided[tiab] OR focused ultrasound[tiab] OR artery occlusion[tiab] OR UAE[tiab] OR morcellat*[tiab] OR electrosurg*[tiab] OR cryoablation[tiab] OR myolysis[tiab]) NOT medline[sb]	16834
#10	#8 OR #9	3075456
#11	#6 OR #7 OR #10	6846698
#12	#3 AND #11	10260

Notes: "Drug therapy"[mh] includes hormone therapy; "Surgical procedures, operative"[mh] includes ultrasound ablation, embolization, and hysterectomy; **Search lines:** #3=uterine fibroid concept; #6 drug treatment concept; #7=therapy or treatment general concept; #10=surgical and procedural interventions concept; #11=any intervention; #12=any intervention or treatment and fibroid

Table 2. Literature search strategy: morcellation and risk of cancer dissemination

	PubMed (3/13/15) Query	Results
#1	morcellation	445
#2	morcellat* AND uterine	256
#3	morcellat*	562
#4	("Electrosurgery/adverse effects"[Mesh]) OR "Uterine Myomectomy/adverse effects"[MeSH] OR morcellat*	1251
#5	("Electrosurgery/adverse effects"[Mesh] AND uterine) OR "Uterine Myomectomy/adverse effects"[MeSH] OR morcellat*	742

Notes: Updated on 10/21/15; retrieved 850 records; After duplicates removed, this literature search update added 103 records.

Grey Literature

We searched web sites of organizations likely to conduct research, issue guidance, or generate policies relevant to management of uterine fibroids and government and regulatory agency web sites for information on morcellation. We searched ClinicalTrials.gov for information about relevant ongoing trials and to confirm that we obtained available publications of results from completed trials.

Scientific Information Packets

The Scientific Resource Center (SRC) issued a notification email to give stakeholders the opportunity to submit a Scientific Information Packet for the topic (i.e., regulatory information on medications, procedures, and devices used to treat uterine fibroids).

Inclusion and Exclusion Criteria

Criteria for the review were derived from our understanding of the literature, refinement of the review topic with the Task Order Officer and Key Informants, and feedback obtained during the public posting period. We included studies evaluating expectant management, pharmaceuticals, procedures, and surgeries to treat fibroids in women of any age. An assessment of the literature suggested that limiting the search to studies published in or after 1985 did not omit critical literature and eliminated a number of treatments that are not used in contemporary care. We detail the acceptable criteria for patients/participants, interventions, comparators, outcomes, timing, and setting (PICOTS) in Appendix B.

For KQ 1 and KQ 2 we restricted the literature to randomized controlled trial (RCTs) evaluating the benefits or harms of a medical, procedural, or surgical intervention compared with an inactive control, including expectant management, placebos, or alternate intervention. We limited inclusion to RCTs because they are superior to cohorts for providing direct evidence about effectiveness and comparative effectiveness of interventions. During topic scoping and refinement of the KQs, we documented a substantial increase in the quality and volume of publications from RCTs since the prior review.[17]

Eligible studies for KQ 1 or KQ 2 had to report one or more patient-centered outcome at baseline and in followup (e.g., symptom improvement, blood loss, pain, quality of life). We did not include studies reporting intermediate outcomes only. Studies reporting only outcomes related to healthcare delivery (e.g., costs, access) were not included. Cost data are linked with operative time and clinician skill sets, which may be affected by a number of factors. Older cost data also have limited utility. We excluded studies in pregnant women. We excluded studies that compared surgical technique or device only (e.g., one type of morcellator vs. a different type). We excluded studies that evaluated a drug not approved for use in the United States except when the study also included a relevant comparator (e.g., studies with a placebo or expectant management comparison arm or an alternate medication approved for use in the United States).

For KQ 3 and KQ 4, we included nonrandomized cohort studies and observational studies that provided data to calculate the proportion of myoma or uterine specimens found to include leiomyosarcoma (KQ 3) or the proportion of women exposed to use of power, sharp, or no morcellation who were followed for dissemination and disease progression of an identified sarcoma. We prioritized an unbiased denominator of women at risk; therefore, cohorts with incomplete documentation of pathology were not included as were studies in which morcellation method was not described.

We conducted a search that would encompass the papers included in a systematic review conducted by Pritts et al. (2015)[18] seeking to update meta-estimates of the risk of encountering a uterine sarcoma at the time of surgical treatment for fibroid tumors. Eligible studies of surgical treatment for fibroids had to report the histology of tumors from all patients. We updated their search and used similar eligibility criteria to identify papers published from six months prior to the end of their search in 2014. We used dual review and prespecified criteria to screen for eligibility. Simultaneously we created a search to identify literature addressing directly the risk of cancerous dissemination and progression following surgery for fibroids, screening papers for data that provided method of removal of the fibroid(s), namely as an intact uterine specimen, using sharp morcellation with a scalpel or other tool, or using power morcellation, and follow-up time with disease and survival status. This literature allowed consideration of characteristics that influence survival including method of surgical removal of the fibroid.

Table 3. Inclusion criteria

Category	Criteria
Population	Women with uterine fibroids (KQs 1-4)
Design	• Randomized controlled trial (KQs 1, 2) • Randomized controlled trials or cohorts (KQs 3, 4)
Other	• Original research (KQs 1-4) • Publication language: English (KQs 1-4) • Publication year: 1985-2015 (KQs 1-4) • Reports one or more: o Patient-centered uterine fibroid treatment/intervention outcome (KQs 1, 2) o Harm or adverse event from uterine fibroid treatment/intervention (KQs 1, 2) o Data to estimate occult leiomyosarcoma prevalence (KQ 3) o Data to estimate risk of leiomyosarcoma dissemination following uterine fibroid treatment (KQ 4) • Sufficient detail of methods and results to enable data extraction (KQs 1-4) • Reports outcome data by target population or intervention (KQs 1-4)

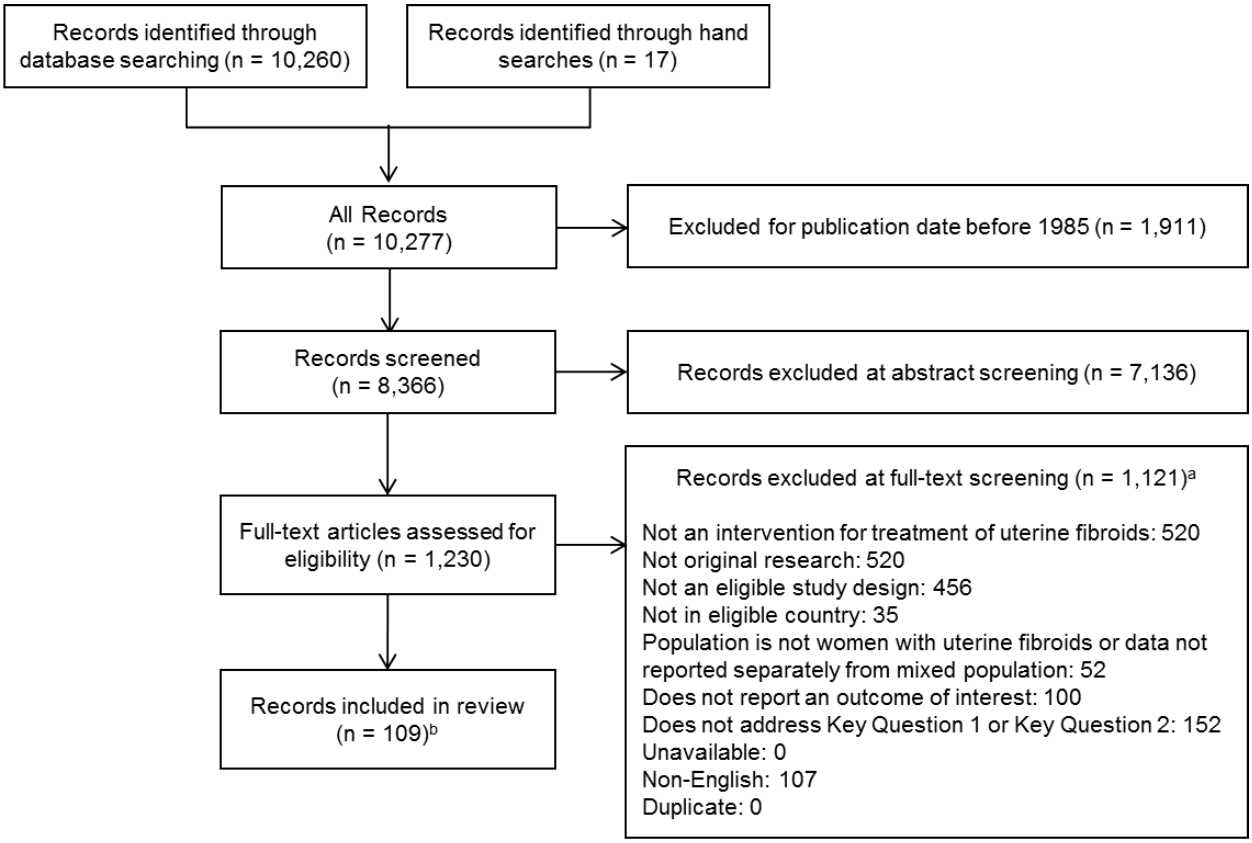
KQ=Key Question

Study Selection

We conducted two levels of screening using dual review and explicit inclusion and exclusion criteria (Table 3). We documented study selection using an abstract screening form and full text screening form (Appendix C). The abstract screening form contained questions about the primary exclusion and inclusion criteria for initial screening. Exclusion of abstract required two team members to classify, independently, the publication as ineligible. We retrieved and reviewed all articles that were not excluded based on the title and abstract screening. We used a more detailed form (full-text screening form) to examine the full-text of references that met criteria for inclusion in abstract review. Two team members independently reviewed eligibility, and, in this case, we resolved conflicting assessments in team discussions.

For KQ 1 and KQ 2, we screened 8,366 records and excluded 7,136 at the time of abstract review. We retrieved the full text of 1,230 publications; 1,121 were excluded for one or more reasons. We identified 110 publications representing 90 unique studies (Figure 2). Appendix D includes a list of excluded publications and reason for exclusion.

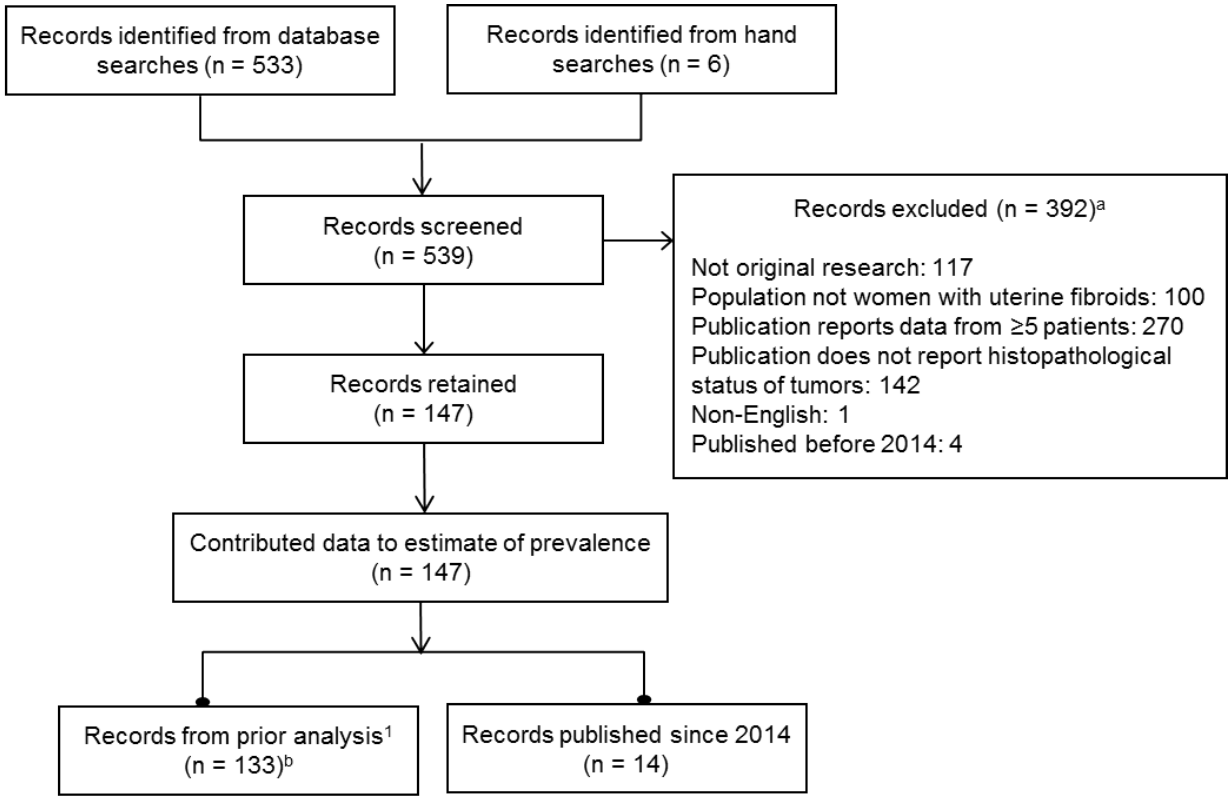
Figure 2. Literature flow diagram for KQ 1 and KQ 2



[a] Records could be excluded for more than one reason. [b] 109 publications representing 90 unique studies.

We identified 147 studies for KQ 3 (Figure 3) and 17 studies (16 of which contributed data to the survival analysis) for KQ 4 (Figure 4) Appendix D includes a list of excluded publications and reason for exclusion.

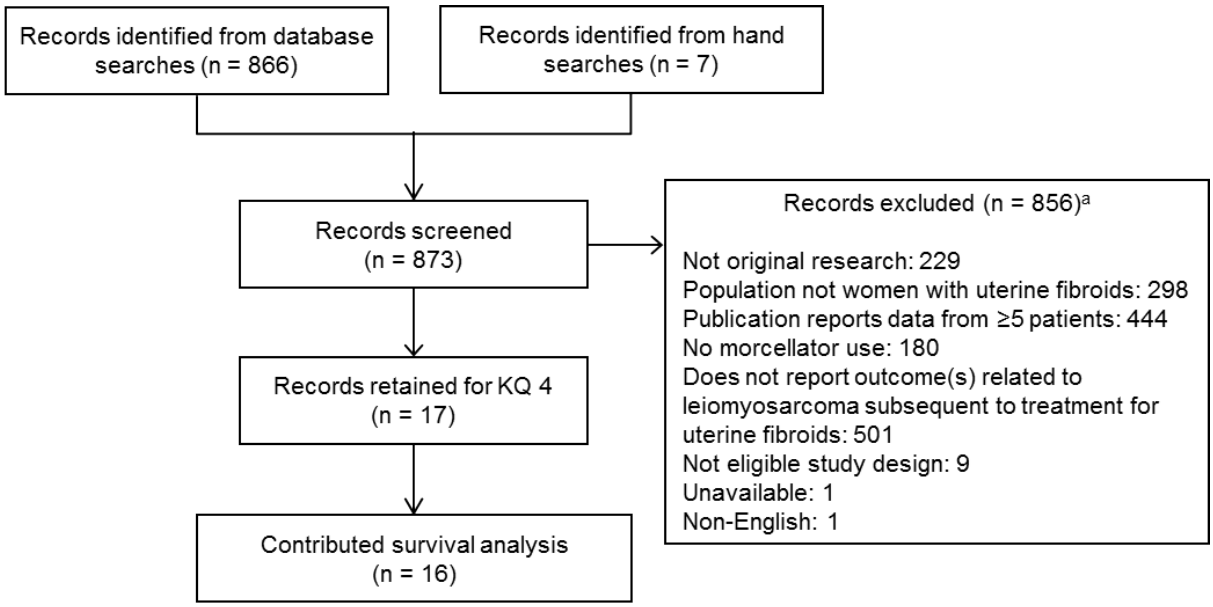
Figure 3. Literature flow diagram for KQ 3



[a] Records could be excluded for more than one reason.
[b] One publication (Silva et al. 2000)[2] contributed data from a retrospective and prospective component. The prior analysis counted the publication as two studies; the publication is counted as one study in the updated analysis.

1. Pritts EA, Parker WH, Brown J, et al. Outcome of occult uterine leiomyosarcoma after surgery for presumed uterine fibroids: a systematic review. J Minim Invasive Gynecol. 2015 Jan;22(1):26-33.
2. Silva BA, Falcone T, Bradley L, et al. Case-control study of laparoscopic versus abdominal myomectomy. J Laparoendosc Adv Surg Tech A. 2000 Aug;10(4):191-7.

Figure 4. Literature flow diagram for KQ 4



[a] Records could be excluded for more than one reason.

In all, we retained 273 publications, representing 253 unique studies to address one or more KQs in this review.

Data Extraction and Management

We created data extraction forms to collect detailed information about study characteristics, participant characteristics, intervention(s), comparator(s), reported outcomes (benefits and harms), tools used for outcome measures, length of follow-up, study results, and elements required for risk of bias assessment. We extracted additional information, when reported, to assess whether the effectiveness of interventions differed by patient or fibroid characteristics.

We assigned codes to document reasons for exclusion and recorded these in an EndNote® (Thomson Reuters, New York, NY) bibliographic database. We used Microsoft Excel to record information about each included publication. Summary tables of study characteristics are presented in Appendix E. We prepared the study outcomes that were used in the meta-analysis for submission to the Systematic Review Data Repository (SRDR).

Outcomes

We extracted the value at baseline, end of treatment, and last followup by arm for each eligible outcome and each measure reported in the paper. For medication treatment, the end of treatment was typically defined by the treatment duration. Surgical and procedural trials often reported estimated blood loss, operative time, length of stay, pain, and transfusion rate. Trials of procedures and medications frequently evaluated need for further intervention and quality of life. Medication studies typically assessed patient symptoms (e.g., pain, uterine bleeding) and fibroid characteristics (e.g., fibroid volume, fibroid size).

We tabulated the incidence of harms and serious adverse events reported in the studies included in KQ 1. We limited extraction of harms to a prespecified list (Figure 1) and recorded the frequency, including "0", during or after the intervention and at last followup.) We extracted these data by arm and did not include comparative rates of harms within studies as studies were not powered to detect differences in harms and did not include sufficient duration of followup. For this same reason, we did not assess the quality of harms reporting within these studies. We categorized the following as serious or major adverse events: death, life-threatening complication, deep vein thrombosis, pulmonary embolism, cardiovascular complication, pulmonary complication, uterine artery dissection.

Outcome Measures

Fibroid Characteristics

Fibroid characteristics may include the number of fibroids left in situ. Some literature relates imaging findings and symptom profiles, but the correlation is not tight. Women with large fibroids can have minimal symptoms, and those with small fibroids may have significant symptoms.

Fibroid-related Bleeding

Measurements of blood loss in the literature vary. Studies reported bleeding characteristics, such as days of bleeding and severity of bleeding as measured by hemoglobin. Changes in bleeding were reported as incidence of amenorrhea, change in bleeding score (on a scale from −5 to +5), and self-reported dysmenorrhea or menorrhagia

Fibroid-related Pain

Myoma-related symptoms including pain, pelvic pressure, urinary frequency, and constipation were measured using a 100-point Visual Analog Scale (VAS). Lower scores are associated with improved symptoms. Some studies assessed pain from self-reported diaries, symptom logs, or by asking patients to grade their pain on a 0 to 5 point scale during followup clinical exams.

Quality of Life

The Uterine Fibroid Symptom and Quality of Life Questionnaire (UFS-QOL) includes 37 patient-reported items across two subscales, the Symptom Severity Scale (8 items) and the HRQoL (29 items).[19] The Symptom Severity Scale measures the variability and severity of menses; it is a 0 to 100 scale, with the higher number representing greater severity of symptoms. The HRQoL component includes subscales to assess 1) concern; 2) activities; 3) energy; 4) mood; 5) control; 6) self-consciousness; and 7) sexual function. The questionnaire responses are measured on a Likert scale from 1 ('none of the time' or 'not at all') to 5 ('all of the time' or 'a very great deal') over a 3-month recall. The UFS-QOL is responsive to treatment for uterine fibroids and is a useful outcome measure for uterine-sparing uterine fibroid treatments.[20] Approximately half of the studies that reported quality of life (9/19) used the UFS-QOL. Higher score on pain, physical aspects, and functional capacity indicate improvement on the SF-36. The EuroQol 5D (EQ-5D) is a score and visual analogue scale to assess preference-based health-related quality of life.

Sexual Function

Sexual function was measured by the following validated instruments: the UFS-QOL, the Brief Index of Sexual Functioning for Women (BISF-W), and the Sexual Activity Questionnaire (SAQ). The USF-QOL uses a scale of zero to 100 and grouped into eight sections, including one section on sexual activity. Higher score indicates an improvement in outcome. The BISF-W consists of 22 questions that measure the following seven aspects of sexual life including desire, arousal, frequency of activity, receptiveness, pleasure/orgasm, relational satisfaction, and problems affecting sexuality. The total scores range from −16 to +75; higher scores indicate higher quality of sexual function with the exception of the problem dimension. The SAQ is a 9-item measure of three dimensions: pleasure from sexual intercourse (desire, enjoyment, and satisfaction), discomfort during intercourse, and habit (frequency). Higher scores for pleasure and habit and lower scores for discomfort are considered good. Total scores range from zero to 27.

Pregnancy and Fertility

To ascertain pregnancy status, publications must, in addition to the number of pregnancies achieved, include the number of participants who wished to become pregnant. Similarly, we considered change in fertility status as an outcome, which includes conversion from myomectomy to hysterectomy in reproductive age women.

Recurrence and Reintervention

We reported reintervention as the sum of all repeat procedures or surgeries (i.e., UAE, myomectomy and hysterectomy) due to any cause, usually complications or technical failure. We reported subsequent treatment for fibroids as those for persistence or recurrence of symptoms and not for complications of the initial intervention.

Quality (Risk of Bias) Assessment of Individual Studies

We evaluated the methodologic quality of studies using risk of bias assessment. We used items and guidance from established tools as described in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[21] We used prespecified items from "Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions"[21] to evaluate the methodologic quality of RCTs. Two senior investigators evaluated each included study independently in six specific domains (Appendix F). Discordance at the level of any domain assignment of risk of bias was resolved through discussion to reach a final adjudicated assignment. We established thresholds to assign an overall rating of "low", "moderate", or "high" risk of bias (Appendix F).[22] Studies with all six domains rated as low risk of bias as well as five with a single fault for not masking those doing imaging when the imaging was MRI, were classified as low risk of bias. For semantic clarity, we refer to these as good quality studies. At the opposite extreme, studies with one or more evaluation domains rated as high or moderate risk of bias, we refer to as poor quality studies. We refer to a study as fair quality, when evaluated to have moderate risk of bias in a single domain.

Data Synthesis

We estimated the probabilities of having additional treatment for fibroids after randomization to a given initial treatment for uterine fibroids. Subsequent treatments were grouped into seven

categories: 1) medical management; 2) MRgFUS; 3) UAE; 4) endometrial ablation with or without hysteroscopic myomectomy; 5) myomectomy; 6) hysterectomy; and 7) no intervention.

We extracted sufficient data to fit models for three initial interventions: UAE, myomectomy, and medical management across mean age for the treatment arm (centered at age 40) and followup time in months (6, 12 or 24 months). Hence, the probability of a subsequent intervention was assumed to be a function of both age and followup time.

As some studies did not report the average age of constituent study arms, we imputed the missing values jointly with the model, using a Student-t distribution to characterize the distribution of ages across studies. Note that this assumes reported ages are missing completely at random and are not omitted for any reason related to the underlying event probabilities.

We fit a binomial random effects meta-analysis, such that event probabilities on the logit scale are normally distributed with mean μ and standard deviation σ. This distribution describes how the probabilities vary across studies, with the degree of variation described by σ.

$$\theta_i \sim N(\mu, \sigma)$$

the expected value for study i is then inverse-logit transformed, and used as the event probability π_i in a binomial model describing the number of observed tumors t:

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \theta_i$$

$$t_i \sim Binomial(n_i, \pi_i)$$

To address the key question, we modeled the parameters θ_i partly as a function of study design and mean age of women in the study arm.

Grading the Strength of Evidence

Strength of Evidence Assessments

We followed *AHRQ EHC Methods Guidance* and updated guidance for grading the strength of a body of evidence.[22,23] We assessed and graded "domains" using established concepts of the quantity and quality of evidence, and coherence or consistency of findings. We focused on evidence that addressed final outcomes in which there was sufficient literature and did not grade all possible outcomes. We assessed strength of evidence for the outcomes reported most frequently (i.e., fibroid volume, fibroid-related bleeding, and quality of life) Two senior staff independently graded the body of evidence; discordance was resolved in meetings of the full team. We assessed strength of evidence for the direction of effect of medical, procedural, and surgical interventions on fibroid volume, bleeding, and quality of life. We assigned an overall evidence grade based on the ratings for the following domains: study limitations; directness; consistency; precision; and reporting bias.

Overall Strength of Evidence

We summarize the four grades (high, moderate, low, and insufficient) we used for the overall assessment of the body of evidence in Table 4 (adapted from the *AHRQ Methods Updated Guidance for Grading the Strength of a Body of Evidence*[22]). When only one study was available for an outcome or comparison of interest, we graded the evidence as insufficient.

Table 4. Strength of evidence grades and definitions [a]

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

[a] Excerpted from Berkman et al. 2013[24]

Applicability

Peer Review and Public Commentary

Researchers and clinicians with expertise in treating uterine fibroids and individuals representing stakeholder and user communities will provide external peer review of this report. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revise the text as appropriate, and document changes and revisions to the report in a disposition of comments report that will be made available 3 months after AHRQ posts the final review on the AHRQ Web site.

Organization of This Report

We have organized the findings about effectiveness for KQ 1 in order from non-invasive interventions (e.g. expectant management or medications), to procedures that can be performed in the office, procedure suite, or as same-day surgery, for instance insertion of intrauterine device (IUD), uterine artery embolization (UAE), or MRI-guided focused ultrasound (MRgFUS), to more invasive surgical interventions that typically require at least a brief hospital stay, such as open myomectomy, hysterectomy.

Within each section summarizing the effectiveness of a category of intervention, or risk of harm from that intervention, we provide data about the influence of that intervention on the final outcomes of interest for this report (Figure 1). When a final outcome, such as influence on fertility, is not discussed it means that the literature did not provide evidence to help understand whether the intervention had any effect on that outcome.

After a summary of four categories of intervention (i.e., expectant management, medications, procedures, and surgeries), we review the results of studies that make direct comparisons across categories (e.g., comparing UAE to hysterectomy). Any comparative information about recovery time, satisfaction with outcomes, and health related quality of life is presented in this context since comparisons across options are useful for women and providers making decisions about care options. At the end of KQ 1, we also provide estimates of the probability of subsequent interventions for fibroids from a model of treatment trajectories developed from the trial data.

We then address the evidence that the effectiveness of intervention (KQ 2) may vary by characteristic of the women or her fibroids. Also, to help inform decision-making, we have indicated across categories of intervention whether a factor, for instance size of fibroids, has more or less influence across intervention options on likelihood of favorable outcomes or harms.

To address KQ 3 and KQ 4, we extended our reach into a larger literature to estimate the risk of cancer dissemination after morcellation, focusing on risk of sarcoma and then on individual and fibroid characteristics that may modify risk of cancer dissemination.

Results

This chapter presents the evidence to address our four Key Questions (KQs): KQ 1, effectiveness of interventions; KQ 2, factors that modify effectiveness; KQ 3, Morcellation of fibroids and risk of uterine sarcoma dissemination; and KQ 4, Patient or fibroid characteristics and risk of uterine sarcoma dissemination following morcellation.

Content of the Literature About Effectiveness

We included 90 unique randomized controlled trials[25-114] and 19 related publications[115-133] (90 studies reported in 109 publications). These studies included 8,331 women with the majority of studies conducted in Europe (Table 5). Forty studies included a pharmaceutical (i.e., medical) intervention;[26,31,35-38,41,49,53,56,57,60,63,65,67,68,71,80,81,85-87,91,92,96,99-103,105-114] 25 assessed a procedural intervention;[25,27,29,30,32,33,39,42-44,47,48,51,52,61,62,69,70,73,76-79,82,90] and 36 assessed surgical treatment.[28,29,34,39,40,42,44-46,50,52,54,55,58,59,64,66,69,72,74,75,77,78,82-84,88,89,93-95,97,98,100,104,110] We included two studies for expectant management arms only, one of tibolone (not approved for use in the United States) versus placebo[102] and one of asoprisnil (not approved for used in the United States) versus placebo.[68] Eleven studies compared interventions from more than one category (e.g., procedure vs. surgery).[29,39,42,44,52,69,77,78,82,100,110]

Table 5. Characteristics of studies included for KQ 1

Characteristic		Med vs. Exp	Med vs. Med	Med vs. Surg	Proc vs. Proc	Proc vs. Surg	Surg vs. Exp	Surg vs. Surg	All
Studies (N)		**13**	**25**	**2**	**16**	**9**	**1**	**24**	**90**
Location	North America*	8	9	0	7	0	0	0	24
	Europe	4	10	2	3	7	1	15	42
	Asia	0	2	0	6	2	0	7	17
	Middle East	1	4	0	0	0	0	1	6
	South America	0	0	0	0	0	0	1	1
Participants	Randomized	917	2,226	114	1,021	962	181	2,910	8,331
Decade of Publication	1985 to 1995	2	6	1	0	0	0	0	9
	1996 to 2005	5	7	1	3	2	0	10	28
	2006 to 2015	6	12	0	13	7	1	14	53
Study Quality	Good	1	1	0	4	1	0	8	15
	Fair	5	7	0	4	4	0	7	27
	Poor	7	17	2	8	4	1	9	48

Abbreviations: Med= medical; Exp= expectant management; Surg= surgical; Proc= procedural; N= number. **Notes:** *Includes studies conducted in the United States, Canada, and Cuba; None of the included studies compared medication with procedure or procedure with expectant management.

We located the study protocol for 16 of the included studies (Appendix G).[26,27,29,35,38-40,47,49,57,60,68-71,78,81] We assessed risk of bias for all studies included for KQ 1. We considered 15 of these RCTs to have low risk of bias (good quality), 27 to have moderate risk of bias (fair quality), and 48 to have high risk of bias (poor quality). The most common shortcoming was failure to blind assessors or participants to treatment status. We enumerate the risk of bias assessments and source of bias for all studies in Appendix F.

Key Question 1. Effectiveness of Treatment for Uterine Fibroids

Key Points

Expectant management

- The number of women in the literature followed without intervention is small and the total picture provided is insufficient to project what the course of watchful waiting may be for an individual woman.

Fibroid size and bleeding characteristics are unlikely to worsen over a short time span (several months).

GnRH agonists

- GnRH agonists reduce the size of fibroids and the overall size of the uterus.
- GnRH agonists, with or without add-back therapy, improve bleeding symptoms, fibroid related pain and other symptoms.
- One study evaluating a GnRH agonist compared medication use to surgical treatment.

HIFU and MRgFUS

- Ultrasound destruction of fibroid tissue reduces fibroid and uterine size.
- Studies reported few other outcomes and focused upon intra and post procedural outcomes (i.e., technical success and safety)
- With the exception of one study that assessed sexual function, publications did not assess symptoms or long-term outcomes.

Hysterectomy technique

- Recovery time to return to work and patient satisfaction were superior with either vaginal hysterectomy or laparoscopic assisted vaginal hysterectomy compared to total abdominal hysterectomy for fibroids
- There are no significant differences in reported harms, comparing techniques for hysterectomy as treatment for fibroids.

Myomectomy technique

- Return to usual activities was sooner following laparoscopic myomectomy compared to laparotomic myomectomy or mini-laparotomic myomectomy.
- No evidence suggests a difference in fibroid recurrence after laparoscopic myomectomy compared to mini-laparotomic myomectomy or laparotomic myomectomy.
- Results for pregnancy outcomes following laparoscopic myomectomy compared to laparotomic myomectomy or mini-laparotomic myomectomy were inconsistent and no technique is clearly superior.
- The benefit of myomectomy for fertility was limited to subjects with removal of submucous fibroids
- There was no significant difference in harms among myomectomy techniques.

Medication versus medication

- No study reported direct comparisons across treatment arms for fibroid symptoms, quality of life, pain, fertility, or uterine bleeding.
- In two studies that evaluated pregnancy outcomes, no study directly compared pregnancy outcomes in the treatment versus control arms.

UAE versus myomectomy

- Compared to myomectomy, length of stay and transfusions were lower after UAE, however, re-intervention rates were higher for women treated with UAE than for those treated by myomectomy.
- Reproductive outcomes were reported to be superior after myomectomy compared with UAE among a subgroup of participants from a small study.
- Quality of life, symptom relief, and fibroid recurrence were similar between UAE and myomectomy groups.
- Incidence of major complications was also similar between groups.

UAE versus hysterectomy

- Compared with hysterectomy, UAE was associated with a shorter hospital stay.
- Re-intervention rates, bleeding symptoms, and need for subsequent treatment were higher among patients treated with UAE versus hysterectomy.
- Changes in quality of life, sexual function, pain, and satisfaction were similar between UAE and hysterectomy groups.
- Although the incidence of major complications was not different, surgical removal of the uterus was associated with more bladder problems, and increased risk for blood transfusion.

Estimation of Subsequent Treatment for Uterine Fibroids

- Probability of subsequent intervention over two years for fibroids varies, ranging from between zero to up to forty percent for following UAE, myomectomy and medical management.

Expectant Management: Overview

We did not identify any studies intentionally designed to determine outcomes of no intervention also called expectant management or watchful waiting. However, 14 RCTs designed for evaluating interventions compared the treatment to no intervention.[36,38,49,60,68,71,72,80,86,91,92,102,109,112] One of these trials one was of good quality, 5 fair, and 8 poor. We summarized the outcomes of women in 14 trial groups that received no treatment, placebo treatment, or minimal intervention such as multivitamin use, with caveats about limitations such as short followup periods and poor tracking of whether women subsequently chose active interventions. Eleven studies had expectant management arms that assessed changes in fibroid or uterine size,[36,49,60,68,71,80,86,91,102,109,112] bleeding patterns (3 studies),[36,49,109] pain, pressure, or symptom severity (6 studies),[36,60,68,71,92,109] sexual function (3 studies),[36,68,109] and pregnancy outcome (1 study).[72]

Expectant Management: Results

Medication trials that included placebo groups contributed virtually all the data about changes in fibroid characteristics and symptoms,[36,38,49,60,68,71,80,86,91,92,102,109,112] along with one study of myomectomy to improve pregnancy outcomes.[72] The studies were small and half (7 of 14) did not report masking those conducting or interpreting the imaging measurements to the status of those in the group not receiving intervention. The placebo-controlled trials did describe credible placebos which diminishes concern that imaging measures would be modified by participant report of their intervention status so unless knowledge of study arm was directly available to those interpreting measures from imaging, the effect of bias may not be substantial.

Expectant Management and Fibroid Characteristics

Overall, the evidence, based on an average followup time of 7 months (range: 3 to 12 months), suggests the size of fibroids does not meaningfully change over short timespans (Table 6).[36,49,60,68,71,80,86,91,92,102,109,112] Neither of the two studies[91,102] with women who were postmenopausal and followed for a full year detected an increase in total volume of fibroids.

Table 6. Change in fibroid and uterine size during expectant management

Author, Year	Group	N	Followup Months Imaging	Fibroid Size Baseline; Followup (cm^3)	Change (cm^3)	Uterine Size	Change (cm^3)
Esteve JL et al. (2013)[36]	Placebo	47	3 (US)	119 ± 96 123 ± 84	↑4.0 p=NR	428 ± 211 439 ± 210	↑11.0 p=NR
Nieman LK et al. (2011)[49]	Placebo	14	3 (MRI)	149 ± 121 159 ± NR	↑10.4 p=NR	NR	NR
Levens E et al. (2008)[60]	Placebo	6	3 (MRI)	290 ± NR 307 ± NR	↑17.4	NR	p=NR
Chwalisz K et al. (2007)[68]	Placebo	31	3 (US)	NR NR	↓4.0% p=NR	NR	↑1.0% p=NR
Fiscella et al. (2006)[71]	Placebo	20	6 (US)	NR	NR	449 ± 236 NR	↑73.0 p=0.37
Jirecek S et al. (2004)[80]	No treatment	12	3 (US)	68 ± 48 78 ± 62	↑10.3 p=0.09	NR	NR
Palomba S et al. (2002)[86]	Multivitamin	29	6 (US)	49 ± 15 55 ± 18	↑6.3 p<0.05	196 ± 57 202 ± 53	↑6.1 p<0.05
Palomba S et al. (2001)[91]	Placebo	35	12 (US)	139 ± 56 NR	No change	317 ± 114 NR	No change p=NS

					p=NS		
Sadan O et al. (2001)[92]	Placebo	10	7 (US)	NR	NR	486 ± NR NR	NR p=NS
Gregoriou O et al. (1997)[102]	No treatment	20	12 (US)	118 ± NR 118 ± NR	↓0.9 p=NS	NR	p=NR
Friedman A et al. (1991)[109]	Placebo injection	64	24 (US/MRI)	206 ± 42 NR	p=NS	492 ± 51 517 ± NR	↑25 p=NS
Friedman A et al. (1989)[112]	Placebo injection	20	6 (US)	NR	NR	426 ± 43 429 ± 52	↑3 p=NS

Abbreviations: N= number of participants; NR= not reported; NS= not significant. US= ultrasound; MRI= magnetic resonance imaging **Notes:** Table does not include Eder S et al. (2013)[38] or Casini ML et al. (2006)[72] as these studies do not report uterine or fibroid size/volume.

Expectant Management and Bleeding

Likewise, bleeding characteristics, such as days of bleeding and severity of bleeding as measured by hemoglobin did not change meaningfully during followup for those without active management (Table 7). Studies that chose other or additional measures also reported no change in outcomes such as in heaviness of periods,[102] monthly hemoglobin measures within normal range,[134] and number and severity of heavy bleeding episodes over 12 months.[91]

Some groups without intervention experienced modest improvements, 6.3 percent of one placebo group had resolution of intermenstrual bleeding over three months[36] Symptom severity score improved slightly in the placebo group after 12 weeks (4.2 ± 6.5).[49] Of 37 women who presented with menorrhagia in the control group of a double-blind study, 26 (70%) reported resolution or improvement at final visit (24 weeks after enrollment).[109]

The proportion of the 457 women enrolled in these trials who presented specifically with problem bleeding, as opposed to other fibroid-related symptoms, is not known. However, the data suggests that women with fibroids should not expect that bleeding patterns will worsen over the near term.

Table 7. Change in bleeding characteristics and hemoglobin with expectant management

Author, Year	Management	N	Followup (months)	Bleeding Baseline; Followup	Change	Hemoglobin Baseline; Followup (g/dl)	Change
Eder S et al. (2013)[38]	Placebo	139	3	177.3 ml 173.0 ml	↓4.3ml p=NR	NR	p=NR
Esteve JLC et al. (2013)[36]	Placebo	47	3	NR	NR	11.8 ± 1.6 11.8 ± NR	p=0.0 p=NS
Nieman LK et al. (2011)[49]	Placebo	14	3	NR	NR	12.3 ± 1.4 12.2 ± 1.1	↓0.1 p=0.82
Levens E et al. (2008)[60]	Placebo	6	3	NR	NR	NR	↓0.9 p=NS
Chwalisz K et al. (2007)[68]	Placebo	31	3	NR	NR	>12.0 NR	↓0.34 p=NR
Fiscella K et al. (2006)[71]	Placebo	20	6	NR	NR	12.2 11.6	↓0.6 p=0.11
Palomba S et al. (2002)[86]	Multivitamin	29	6	3.9 ± 1.3 4.0 ± 1.3 days	↓0.1 p=NS	13.9 ± 1.7 13.8 ± 1.6	↓0.1 p=NS
Palomba S et al. (2002)[86]	Multivitamin	29	6	6.1 ± 2.1 6.0 ± 2.1 days	↓0.1 p=NS	NR	p=NR

Author, Year	Management	N	Followup (months)	Bleeding Baseline; Followup	Change	Hemoglobin Baseline; Followup (g/dl)	Change
Sadan O et al. (2001)[92]	Placebo	10	7	NR	NR	NR	↑1.0% NS
Friedman AJ et al. (1991)[109]	Placebo injection	64	6	NR	NR	12.6 ± 0.3 12.3 ± 0.2	↓0.3 p=NR
Friedman A et al. (1989)[112]	Placebo injection	20	6	NR	NR	12.3 ± 0.3 11.3 ± 0.6	↓1.0 p=NS

Abbreviations: g/dL=grams per deciliter; mL=milliliters; NR= not reported; NS= not significant

These findings of minimal change over followup periods of a year or less are compatible with a prior review that included observational cohorts.[17] The number of women in the literature followed without intervention is small and the total picture provided is insufficient to project what the course of watchful waiting may be for an individual woman. Because none of these studies were designed to evaluate expectant management, the overall quality of the research is poor to inform choice of expectant management over other options and strength of the evidence is low.

Pharmaceutical Management: Overview and Nomenclature

The etiology of uterine fibroids is poorly understood and therapies targeted to specific biological mechanisms that cause fibroids are not available. As an overarching principal, pharmaceutical interventions rely on disrupting hormonal stimulus to fibroids. Initially medications were primarily studied as a short-term treatment for use as preparation for surgery to reduce anemia and to decrease size of fibroids thereby facilitating operative removal. We did not review these adjunctive treatments in trials in which all participants were scheduled to proceed to surgery as GnRH analogues have been shown to be effective for minimizing blood loss at the time of surgery and decrease fibroid growth prior to surgery.[135]

We sought studies that addressed whether medications can serve as an alternative to surgery or sufficiently resolve symptoms to delay the need for other management. Our intended scope was wide, including common clinical interventions such as use of oral contraceptives continuously to avoid menstrual periods, non-steroidal anti-inflammatory agents to improve bleeding characteristics or dysmenorrhea, and agents such as stool softeners to prevent constipation from bulky fibroids. RCTs identified reflect clinically less common medications in three major groups:

- **GnRH agonists** were the subject of 16 studies, which included eight with addition of a second agent to a GnRH agonist.
- Seven studies evaluated **progestin antagonists** and four of **progesterone receptor modulators** as well as a single trial of a progesterone-containing IUD
- Four studies[80,86,91,92] reported **estrogen-receptor modulators**.

For convenience and consistency, we briefly describe the medications evaluated below. We have included review of medications available for prescribing in the United States.

GnRH Agonists and Adjuncts. GnRH agonists induce varied degrees of "medical menopause". This down-regulates production of estrogen and progesterone and decreases stimulation of hormone receptors, which decreases fibroid growth and may promote involution. This class of agents also causes absence of menses and this can improve anemia associated with heavy bleeding from fibroids. Adjuncts or add-back therapy may be used with a GnRH agonist to offset unwanted side effects such as hot flashes, vaginal dryness, and decreased in bone density.

Leuprolide is a potent inhibitor of gonadotropin secretion. Trade names include Eligard®, Lupron Depot-Ped®, Lupron Depot®, Lupron®, and Viadur®. Leuprolide can be used as an alternative to surgery or other interventions for fibroids. Its potent effect on reducing estrogen activity in the uterus is intended to decrease fibroid size and reduce symptoms including menorrhagia. Thirteen RCTs included a leuprolide treatment group, seven with an add-back agent.

Goserelin (Zoladex®) is also a potent inhibitor of gonadotropin secretion with similar mechanisms. Three studies[65,100,111] included a goserelin treatment group, one to assess feasibility of using goserelin to treat symptoms and delay need for surgery,[100] and two included evaluation of add-back agents not in use in the United States (tibolone[65] and buserelin[111]). These add-back studies are included in order to include the findings in the goserelin only groups.

Triptorelin, trade names Decapeptyl® and Gonapeptyl®, is most used in the United States to treat advanced prostate carcinoma. Its activity on fibroids and use for fibroid management is similar to other GnRH agonists. Two studies included a triptorelin treatment group.

Progesterone receptor agents: anti-progestins, partial agonists, and locally released progesterone. These agents bind to a progesterone receptors and modulate function with the intention of decreasing progesterone activity and reducing the size of fibroids.

Mifepristone (Mifeprex®) is a synthetic steroid that competitively binds to the intracellular progesterone receptor. It blocks the effects of progesterone and can cause reduction in the size of fibroids. Mifepristone also exhibits antiglucocorticoid activity, which may limit long term use.

Ulipristal acetate (Ella®, Esmya®) is a selective progesterone receptor modulator which binds the human progesterone but not the estrogen receptor. Ulipristal is structurally similar to mifepristone, but has less antiglucocorticoid activity, suggesting it is better alternative to mifepristone for long term use.[60,136,137] It has been FDA approved since 2010 for emergency contraception. The European Medicines Agency granted marketing authorization for ulipristal acetate, 5 mg (Esmya, Preglem/Gedeon Richter) for long term medical management and preoperative therapy in reproductive age women with uterine fibroids.

LNG-IUD contains 52 mg 19-norprogestterel levonorgestrel and 20 µgr of levonorgestrel is released daily. It reduces bleeding time by inhibiting endometrial proliferation.

Estrogen receptor agents: modulators and antagonists. Selective estrogen receptor modulators (SERMs) are synthetic molecules that bind to estrogen receptors to mimic or block estrogen activity. Some are designed to have differential effects across tissue types (e.g., bone, brain, and liver) to target action of the drug and reduce side effects.

Raloxifene (Evista®) was designed as a tissue-targeted menopausal hormone therapy; it does not alleviate, and may worsen, vasomotor symptoms associated with menopause. In the treatment of fibroids, raloxifene is used to promote reduction in fibroid size.

Tamoxifen was introduced to block estrogen action in the treatment of breast cancer. Tamoxifen is also used with the goal of stabilizing or reducing fibroid size.

Pharmaceutical Management: Results

We identified 40 studies assessing effectiveness of pharmaceutical treatment for uterine fibroids.[26,31,35-38,41,49,53,56,57,60,63,65,67,68,71,80,81,85-87,91,92,96,99-103,105-114] Nine studies included a placebo or no treatment comparison group[36,38,60,71,80,91,92,109,112] to assess effectiveness of pharmacologic treatment for management of uterine fibroids. Seven studies compare two or more medications[53,56,67,87,96,99,111] and 10 compared doses of the same drug.[26,35,37,41,49,57,81,86,103,108] Several studies evaluated dose schedules or regiments that change over time. Another eight

studies[63,65,85,101,105-107,113] examined the role of an additional drug given to decrease the side effects of the primary treatment (i.e., add-back). Eight studies that included a medical intervention are discussed in other sections of this report: two studies, one of tibolone (not approved for use in the United States) versus placebo[102] and one of asoprisnil (not approved for used in the United States) versus placebo,[68] are discussed in the section on expectant management; four studies[53,67,87,99] are discussed in the section on comparison of effectiveness across intervention categories; and two studies that compared a GnRH agonist to surgery[100,110] are summarized in the surgical intervention section.

We have organized this section to first present the evidence about effectiveness for each category of drug with an emphasis on summarizing outcomes across studies when an important outcome has been measured by multiple studies. We also note if several specific doses or routes of delivery of the drug, for instance injection vs. oral, have been investigated. We reserve discussion of direct comparisons between categories of medications to the end of the section. We have excluded information about medications that cannot be prescribed in the United States, unless there was an FDA application for approval pending.

Approximately 30 percent of the medication studies (13/40) were industry sponsored.[26,31,35-38,41,65,68,100,103,105,109] The longest duration of followup after the end of treatment was 36 months in one study.[100] The duration of followup ranged from no additional followup after the end of treatment with the medication to 12 months after conclusion of the medication. Women included in the studies were predominately premenopausal (36 studies). Four studies[87,91,99,102] enrolled postmenopausal women.

To summarize outcomes we move from changes in the fibroids, to changes in symptoms, including bleeding characteristics, pain, and sexual function. When reported we also summarize fertility status and pregnancy outcomes as well as satisfaction with treatment and subsequent treatments over time. Only hemoglobin/hematocrit laboratory values, severity of uterine bleeding, and standardized quality of life and functional status measures were reported using validated approaches.

We rated two RCTs as good quality (low risk of bias), 12 as fair (moderate risk of bias), and 26 as poor quality (high risk of bias). Common reasons for classification as poor quality included: no description or unclear description of randomization method (4 studies),[65,80,101,107] no report of assessment of medication adherence,[91] and failure to blind outcome assessors.[63,65]

GnRH Agonists

Eighteen publications from 16 studies evaluated GnRH agonists.[56,63,65,85,96,100,101,103,105-109,111-113,132,133] The studies are small with an average of 59 (1,065 total) participants, the earliest in 1988 included 16 women,[107] the largest published in 1991 enrolled 128 women[109] and the second largest, published in 2008, 110 women.[63] This small study size limits power for discerning differences across treatment groups and virtually prohibits meaningful evaluation of factors that may influence outcomes within groups. In general, study size was selected to detect differences in fibroid size and bleeding characteristics that are measured as continuous variables. The clinical significance of small to modest changes in fibroid size is unknown. No studies were specifically designed to assess if treatment improved patient reported outcomes such as improvements in quality of life, sexual function, or satisfaction with treatment.

As in much of the fibroid literature, lack of followup over time is a limitation. Most studies completed their followup of participants at the same time as treatment with the medication or placebo stopped. With the exception of six studies[65,108,109,111,112,133] that followed women from 3

to 6 months after end of treatment we have no information about how durable the effects may be. Only one study recontacted participants years after treatment to investigate what their treatment choices had been over time.[100]

Effects of GnRH Treatment on Fibroid Characteristics

GnRH agonists reduce the size of fibroids, with reductions in volume of fibroids documented between 64 and 175 cm^3 and reductions in the total volume of the uterus between 131 and 610 cm^3 (Table 8). As a point of reference, the volume of a golf ball is 40 cm^3. It may be that change in size is related to initial size, in other words bigger fibroids have more capacity to shrink and these studies are not able to assess if that is the case. Likewise, the duration of treatment cannot be directly related to reduction in volume. Two studies that measured fibroids more than once across the course of treatment found the change in the first round of imaging to be the greatest.[108,109]

Table 8. Change in fibroid and uterine size with GnRH treatment

Author, Year	Dose	N	Rx Months	Last Followup	Fibroid Size Baseline; Followup (cm^3)	Change, cm^3	Uterine Size Baseline, cm^3 Followup, cm^3	Change (cm^3)
Goserelin								
Morris E et al. (2008)[65]	3.6 mg SQ each month	23	6	12	NR	↓60.9 ± 3.3% p<0.05	NR	↓57.9 ± 2.1% p<0.05
Costantini S et al. (1990)[111]	3.6 mg SQ each month	21	6	12	192 ± 126 98 ± 86	↓94 p=NR	253 ± 52 122 ± 50	↓131 p=NR
Leuprolide								
Palomba S et al. (2008)[63]	11.25 mg IM each 3 months	55	6	6	NR	NR	565 ± 89 NR	↓NR p<0.05
Palomba S et al. (2002)[85]	3.75 mg SQ each month	50	6	6	189 ± 54 (M) NR	↓NR p<0.05	446 ± 105 NR	↓NR p<0.05
Takeuchi H et al. (2000)[96]	1.88 mg SQ each month	33	5.2	5.2	172 ± 166 (L) 108 ± 139 (L)	↓64 p<0.01	NR	NR
Palomba S et al. (1998)[101]	3.75 mg SQ each month	25	6	6	308 ± 65 133 ± 34	↓175 p<0.01	996 ± 170 386 ± 95	↓610 p<0.01
Scialli A et al. (1995)[105][1]	3.75 mg SQ each month	32	6	6	NR	NR	454 ± 102 195 ± 36	↓259 p<0.05
Carr B et al. (1993)[107]	1 mg SQ each day	9	3	5.5	345 ± 177 301 ± 161	↓44 p=NS	1278 ± 205 937 ± 188	↓341 p<0.04
Watanabe Y et al. (1992)[108]	1.88 mg SQ each month	20	5.5	12	NR NR	↓54.0% (n=9) p<0.01	553 ± 499 295 ± 351	↓258 p<0.01

[1] Uterine volume at baseline and after 6 month of leuprolide treatment among 32 individuals from both arms.

Author, Year	Dose	N	Rx Months	Last Followup	Fibroid Size Baseline; Followup (cm^3)	Change, cm^3	Uterine Size Baseline, cm^3 Followup, cm^3	Change (cm^3)
Watanabe Y et al. (1992)[108]	3.75 mg SQ each month	21	5.5	12	NR NR	↓43.0% (n=7) p<0.01	452 ± 224 271 ± 314	↓181 p<0.01
Friedman A et al. (1991)[109]	3.75 mg SQ each month	60	5.5	12	143 ± 43 (L) 86 ± NR (L)	↓57 p<0.001	522 ± 52 289 ± NR	↓233 p<0.001
Friedman A et al. (1989)[112]	3.75 mg SQ each month	18	6	9	NR	NR	505 ± 93 305 ± 57	↓200 p<0.05
Friedman A et al. (1993)[106]	3.75 mg SQ each month	51	3	12	NR	NR	820 ± 127 NR	↓36.0% p<0.05
Friedman A et al. (1988)[113]	0.5 mg SQ each day	7	5.5	6	NR	NR	601 ± 62 294 ± 46	↓307 p<0.01
Triptorelin								
Parsanezhad ME et al. (2010)[56]	3.6 mg SQ each month*	27	2.8	2.8	95 ± NR 64 ± NR	−33.2% p=0.02	NR	NR
Broekmans FJ et al. (1996)[103]	500 mg x 1 wk, 100 mg x 7 wks, variable dose (5, 20, or 100 mg) x 18 wks	24	1.8	6.5	NR	↓31.1% p≤0.001	931 ± NR 692 ± NR	↓239 p≤0.001
		24	6		NR	↓36.1% p≤0.001	931 ± NR 525 ± NR	↓406 p≤0.001

Notes: Parazzini F et al. (1999)[100] only reports baseline number/size of fibroids for goserelin (n=59). **Abbreviations:** cm=centimeter; NR=Not reported; IM=Intra muscular; L= largest ; M= mean; mg=milligrams; n=number; NR=not reported; wk=week; SQ=Subcutaneous ; Rx=treatment ;

Five studies provided information on durability of treatment effects from 3 to 6 months after the end of treatment.[108,109,111,112,133] All 5 studies that reassessed uterine and/or fibroid volume reported increases or regrowth often back to pre-treatment levels.[108,109,111,112,133] A single study evaluated two different doses (1.88 mg and 3.75 mg) of GnRH and reported they were equally effective in reducing uterine volume.[108] Use of add back therapies to reduce the side effects of GnRH agonists did not prevent the desired effect of decreases in fibroid size.[85] Add-back therapy of tibolone was protective for bone mineral density without interfering with fibroid size reduction.[65]

Effects of GnRH Treatment on Bleeding

GnRH agonists are designed to shut down the production of the hormones that result in menstrual cycles – they create a temporary medical menopause. As a result, the effects on bleeding are substantial (Table 9). Because many women completely stop bleeding, the decrease in days is not as often reported. In total five studies reported absence of bleeding, three noting statistical significance for clinically important reduction from baseline. One study reported reduction in days of bleeding[65] without a statistical test and four reported improvement in

hemoglobin levels with three of the four reporting significance. No study reported an increase in bleeding or worsening in measures such as hemoglobin or hematocrit within a treatment group though individual women in several studies discontinued treatment because bleeding became more irregular or did not decrease.

Add-back therapy was evaluated in eight studies. Women who received medroxyprogesterone (MPA) as add-back therapy in conjunction with GnRH agonist had improved hemoglobin levels reported in two small trials. [105,113] A single trial that evaluated raloxifene as add-back therapy in conjunction with leuprolide acetate noted that only three (6.3%) of women receiving raloxifene and four (8.3%) women receiving placebo continued to bleed after six cycles of therapy.[85] Another small study that compared estrogen-progestin to progestin only add-back with leuprolide acetate depot reported improved hemoglobin levels in both groups.[106] Add-back therapy with tibolone (not currently approved by the FDA for use in the United States) was evaluated in three placebo-controlled trials.[63,65,101] Women receiving tibolone in conjunction with goserelin had significantly higher mean number of days of bleeding (6.3 days) compared to only 2.9 days in the goserelin and placebo group.[65] In another 6-month study of leuprolide acetate, both groups had reductions in the number of women reporting bleeding, but a small number of women continued to bleed with the add-back of tibolone compared to none in the placebo arm.[101] Bleeding outcomes were not assessed in the third study.[63]

Table 9. Change in bleeding characteristics and hemoglobin with GnRH agonist therapy

Author, Year	Dose	N	Rx Months	Followup Time, months	Bleeding Baseline; Followup	Change	Hemoglobin Baseline; Followup (g/dl)	Change
Goserelin								
Morris E et al. (2008)[65]	3.6 mg implant each month	23	6	12	4.3 days 2.9 days	NR	NR	NR
Costantini S et al. (1990)[111]	3.6 mg SQ each month	21	6	12	NR 0 days by 8 weeks	NR	NR	NR
Leuprolide								
Palomba S et al. (2008)[63]	11.25 mg IM each 3 months	55	6	6	Menorrhagia* 7.7 ± 1.6 0.0 ± 0.0	p=0.001	NR	NR
Palomba S et al. (2002)[85]	3.75 mg SQ each month	46	5.5	6	7.8 ± 1.9* 0.0 ± 0.0	p<0.05	NR	NR
Palomba S et al. (1998)[101]	3.75 mg SQ each month	25	6	6	8.2 ± 0.9* 0.0 ± 0.0	p<0.01	NR	NR
Scialli A et al. (1995)[105]	3.75 mg SQ each month	14	12	12	NR	NR	10.3 ± 0.8 11.2 ± 0.6	↑0.9 p<0.05
Watanabe Y et al. (1992)[108]	3.75 mg SQ each month	21	5.5	12	0 days by 4 weeks	NR	NR	NR
Friedman A et al. (1991)[109]	3.75 mg SQ each	60	5.5	12	NR	NR	12.6 ± 0.2 13.1 ± 0.2	↑0.5 p<0.05

Author, Year	Dose	N	Rx Months	Followup Time, months	Bleeding Baseline; Followup	Change	Hemoglobin Baseline; Followup (g/dl)	Change
	month							
Friedman A et al. (1989)[112]	3.75 mg SQ each month	18	6	9	NR	NR	12.3 ± 0.4 13.0 ± 0.3	↑0.7 NS
Friedman A et al. (1988)[113]	0.5 mg SC each day	7	5.5	6	NR	NR	12.7 ± 0.3 14.1 ± 0.2	↑1.4 p<0.001

Notes: *Menorrhagia score, values from 0 to 10 where 0 indicates no bleeding. **Abbreviations**: IM= Intramuscular; mg=milligrams; NR=Not reported; NS=Not significant; SQ= Subcutaneous

Effect of GnRH Treatment on Fibroid Related Pain

Pain symptoms improved by GnRH treatment included pelvic pressure,[63,65,85,133] pelvic and abdominal pain,[63,65,85,133] and dysmenorrhea.[65] Other studies reported similar improvements but without statistical comparisons of baseline to followup.[106,109]

Other Treatment Effects of GnRH Treatment

Palomba and colleagues have conducted multiple studies treating women for six months with leuprolide and placebo (the comparator arm included a medication not available in the United States).[63,85,101] Within the leuprolide arms of these studies, women experienced a significant improvement in fibroid related symptoms that were scored on a 1 to 10 point validated scale that includes menorrhagia, pelvic pressure, pelvic pain, urinary frequency, and constipation. Total scores and each individual scale item were improved, in each study bleeding and constipation completely resolved and other scores improved by 3 to 5 points, a substantial and likely clinically significant change. Mood and quality of life were also improved by treatment.[63] In studies with raloxifene add-back, similar improvements have been documented in both the raloxifene and placebo add-back groups.[85]

Using a similar, but not identical 5-item scale, Friedman and colleagues, also demonstrated improvement in menorrhagia, bulk symptoms, pelvic pressure, urinary frequency and pelvic pain that were sustained over one and two years of treatment with leuprolide and either estrogen and progestin add-back or just progestin add-back; with an overall advantage for the combined estrogen and progestin add-back group.[106,133]

Potential Harms of GnRH Treatment

Because of suppression of estrogen, GnRH is associated with onset of menopausal symptoms,[63,65,101,109] unfavorable changes in lipid profile,[101,106] and bone loss,[101] ranging from 2.6 percent[133] to 5.5 percent [65] in these studies. These effects increase motivation for investigating add-back therapy. Estrogen and progesterone together normalize adverse lipid effects, while progesterone only did not.[106] Addition of raloxifene protects bone[101] and estrogen-progestin or progestin add-back stabilized bone loss when initiated after a 12-week period of GnRH only.[106]

Six months of treatment with leuprolide was associated with declines in cognitive function and memory as measured by the Mini-mental Status Exam and the Wechsler Memory Scale. This was remediated in the comparison group by add-back with tibolone (a drug not reviewed since it is not available for prescription in the United States).[63]

GnRH Agonists Summary

GnRH agonists reduce the size of fibroids and the overall size of the uterus. Both with and without add-back therapy bleeding symptoms are improved and anemia or baseline blood count is improved, likewise fibroid related pain and other symptoms improve both with single agent treatment and with add-back treatment. Add-back medication relieves associated menopausal symptoms and can ameliorate bone loss and lipid changes. Only one trial examined outcomes of treatment after more than 24 months.[133] This study found that effects can be maintained over two years. Seventeen of 51 women discontinued treatment during that time, three for other medication options, five had myomectomies, and nine had hysterectomy. Extended followup of women after they discontinue GnRH agonists is not available, thus information about potential harms is limited to guide care.

Progesterone Antagonist, Selective Receptor Modulators and Intra-uterine Progesterone Treatments

This section includes 12 studies designed to test the effectiveness of medications that work through progesterone pathways.[26,31,35-37,41,49,57,60,71,81,114] They include seven studies of mifepristone,[35-37,41,57,71,81] which is a progesterone antagonist that blocks the action of progesterone; four of ulipristal[26,31,49,60] a progesterone receptor modulator that selectively promotes shrinkage of fibroid cells; and a single study of a progesterone containing intrauterine device (IUD)[114] that aims to reduce bleeding associated with fibroids by causing atrophy of the endometrial lining.

Mifepristone

Seven studies (eight publications) provide data about outcomes of mifepristone treatment.[35-37,41,57,71,81,131] This literature is dominated by two teams: a group led by Carbonell and colleagues who conducted five of the included studies in Cuba, and two more studies done at University of Rochester School of Medicine by Eisinger and Fiscella.[71,81,131] Racial diversity is notable at the Cuban sites while the Rochester site under-represents the proportion of African American women with fibroids in the United States.

Two studies compared a 5 mg dose to placebo,[36,71] one study compared 2.5 mg and 5 mg doses,[35] the remainder compared 5 mg and 10 mg doses. Four groups included followup after treatment with mifepristone had ended. Average length of time for off-medication followup was 11 months with the longest untreated followup being 12 and 18 months.[37,138]

Effects of Mifepristone on Fibroid Characteristics

All studies observed a decrease in the size of fibroids at the completion of the period of active treatment (Table 10). The magnitude of change in size of the largest fibroid ranged from a decrease of 37 cm^3 to 95 cm^3, with an average of 71 cm^3 among the 575 women studied.[35-37,41,57] Likewise, total uterine volume decreased in all groups receiving mifepristone.[35-37,41,57,71,81,131] This was consistent across doses from 2.5 mg to 10 mg each day, with statistically significant reductions at 5 mg and 10 mg doses documented in three trials.[57,71,81] Because most trials were designed to compare doses, authors often did not provide statistical comparisons within groups from baseline to followup.

In the studies designed to determine if changes in fibroid size were durable, all four trials reported no statistically meaningful change in the size of the largest fibroid or uterine volume

after completion of treatment.[35,37,41,131] However in review of the measures it is intriguing to note that while volume of the largest fibroid remained smaller than baseline at nine months of followup of medication, the total uterine volume was slightly increased over baseline. With 12 and 18 months of followup, fibroid and uterine volume tended to increase, often above baseline,[37,41] suggesting that treatment suspends fibroid growth but does not have lasting "programming" effects to forestall future growth of the same or new fibroids.

It is also important to note in these studies that the number of women available at followup was often lower than initial enrollment. This loss to followup includes those who did not continue medication or who did not improve and had subsequent treatments including surgery. Since intention-to-treat analyses with last uterine volume carried forward were not done, this means as the number of women available falls, the measures may under-represent changes in fibroids if we speculate that those who were lost could be more likely to have increase in size over time.

Table 10. Mifepristone therapy and change in fibroid and uterine size

Author, Year	Daily Oral Dose	N	Rx Months	Fibroid Size Baseline; Followup(s) (cm^3)	Change (cm^3)	Uterine Size Baseline; Followup (cm^3)	Change (cm^3)
Carbonell JL et al. (2013)[35]	2.5 mg no dose during 9 month followup	102	3	136 ± 129 (L) 98 ± 107 (L)	↓38 p=NR	455 ± 314 372 ± 272	↓83 p=NS
		90	12	136 ± 129 (L) 129 ± 157 (L)	↓7 p=NS	455 ± 314 495 ± 321	↑40 p=NS
Carbonell JL et al. (2013)[35]	5 mg no dose during 9 month followup	106	3	112 ± 118 (L) 60 ± 67 (L)	↓62 p=NR	426 ± 305 332 ± 243	↓94 p=NS
		100	12	112 ± 118 (L) 99 ± 91 (L)	↓13 p=NS	426 ± 305 489 ± 265	↑40 p=NS
Carbonell JL et al. (2013)[36]	5 mg	58	3	125 ± 95 (L) 88 ± 79 (L)	↓37 p=NR	458 ± 236 354 ± 202	↓104 p=NR
Carbonell JL et al. (2013)[37]	5 mg no dose during 18 month followup	31	9	115 ± 100 (L) 55 ± 41 (L)	↓60 p=NR	542 ± 362 361 ± 175	↓181 p=NR
		9	27	115 ± 100 (L) 169 ± 86 (L)	↑54 p=NS	542 ± 362 715 ± 433	↑173 p=NS
Carbonell JL et al. (2013)[37]	10 mg no dose during 18 month followup	34	9	263 ± 471 (L) 90 ± 77 (L)	↓38 p=NR	866 ± 578 533 ± 570	↓333 p=NR
		12	27	263 ± 471 (L) 255 ± 156 (L)	↓8 p=NS	866 ± 578 892 ± 412	↑26 p=NS
Carbonell Esteve JL et al. (2012)[41]	5 mg no dose during 12 month followup	74	6	133 ± 176 (L) 81 ± 102 (L)	↓52 p=NR	573 ± 480 417 ± 271	↓156 p=NR
		74	18	133 ± 176 (L) 138 ± 117 (L)	↑5 p=NS	573 ± 480 666 ± 219	↑93 p=NS
Carbonell Esteve JL et al. (2012)[41]	10 mg no dose during 12 month followup	70	6	108 ± 103 (L) 56 ± 61 (L)	↓52 p=NR	544 ± 353 379 ± 259	↓165 p=NR
		70	18	108 ± 103 (L) 128 ± 108 (L)	↑20 p=NS	544 ± 353 596 ± 299	↑52 p=NS
Carbonell Esteve JL et al. (2008)[57]	5 mg	50	3	172 ± 161 (L) 77 ± 125 (L)	↓95 p<0.001	481 ± 257 305 ± 192	↓176 p<0.001

Author, Year	Daily Oral Dose	N	Rx Months	Fibroid Size Baseline; Followup(s) (cm^3)	Change (cm^3)	Uterine Size Baseline; Followup (cm^3)	Change (cm^3)
Carbonell Esteve JL et al. (2008)[57]	10 mg	49	3	187 ± 184 (L) 103 ± 124 (L)	↓84 p<0.001	552 ± 499 332 ± 200	↓220 p=0.002
Fiscella K et al. (2006)[71]	5 mg	22	6	NR	NR	719 ± 663 519 ± NR	↓200 p=0.02
Eisinger SH et al. (2003)[81]	5 mg	19	6	NR	NR	832 ± 443 435 ± NR	↓397 p<0.001
Eisinger SH et al. (2003)[81]	10 mg	20	6	NR	NR	850 ± 380 438 ± NR	↓412 p<0.001

Notes: Eisinger SH et al. (2005)[131] reports similar results (52-53% reduction in uterine volume) for 12 months of treatment, but combines 5 mg and 10 mg groups. **Abbreviations:** cm=centimeter; mg=milligrams; n= number NR=Not reported; NS=Not significant; L= largest.

Effects of Mifepristone on Bleeding

All studies that assessed bleeding (Table 11) reported heaviness of bleeding was reduced by treatment. Those that made comparison to placebo found active drug superior.[36,71] Women were more or equally likely to have decreased bleeding or absent menses on the lower doses compared to the higher doses.[37,57,131] When bleeding occurred it was often described as spotting or staining.[35,36,41]

Table 11. Change in bleeding characteristics and hemoglobin with mifepristone treatment

Author, Year	Daily Oral Dose	N	Months	Bleeding Measure	Baseline Followup	Change
Carbonell JL et al. (2013)[35]	2.5 mg	102	3	Percent with hemoglobin <10g/gl	37.3% 14.7%	p=0.02
Carbonell JL et al. (2013)[35]	5 mg	106	3	Percent with hemoglobin <10g/gl	40.9% 6.6%	p=0.02
Carbonell JL et al. (2013)[36]	5 mg	58	3	Hemoglobin (g/dl)	11.0 ± 2.0 11.7 ± 2.1	↑0.7 p=0.023
Carbonell JL et al. (2013)[37]	5 mg	31	9	Percent with amenorrhea	NR 100.0%	NR
Carbonell JL et al. (2013)[37]	10 mg	34	9	Percent with amenorrhea	NR 80.0%	NR
Carbonell Esteve JL et al. (2012)[41]	5 mg no med 12 month	74 74	6 18	Hypermenorrhea score	8.3 ± 2.2* 0.1 ± 0.5 6.6 ± 2.2*	p<0.01*
Carbonell Esteve JL et al. (2012)[41]	10 mg no med 12 month	70 70	6 18	Hypermenorrhea score	8.9 ± 1.8* 0.1 ± 0.3 6.2 ± 2.6*	p<0.01*
Carbonell Esteve JL et al. (2008)[57]	5 mg	50	3	Hypermenorrhea percent	78.0% 4.0%	NR
Carbonell Esteve JL et al. (2008)[57]	10 mg	49	3	Hypermenorrhea percent	66.0% 6.1%	NR
Carbonell Esteve JL et al. (2008)[57]	5 mg	50	3	Percent with amenorrhea	NR 90.0%	NR
Carbonell Esteve JL et al. (2008)[57]	10 mg	49	3	Percent with amenorrhea	NR 89.8%	NR

Author, Year	Daily Oral Dose	N	Months	Bleeding Measure	Baseline Followup	Change
Fiscella K et al. (2006)[71]	5 mg	22	6	Hemoglobin (g/dl)	12.0 13.5	↑1.5 p<0.001
Eisinger SH et al. (2003)[131]	5 mg	19	6 12	Percent with amenorrhea	0% 63.0% 75.0%	NR
Eisinger SH et al. (2003)[131]	10 mg	20	6 12	Percent with amenorrhea	0% 60.0% 40.0%	NR

Abbreviations: mg=milligrams; n=number; NR=Not reported; g/dl=Grams per deciliter

Effects of Mifepristone on Fibroid-Related Pain

Each of six publications that evaluated pelvic pain before treatment and at conclusion of treatment noted substantial improvements.[35-37,41,57,71] At baseline more than 68 percent up to 100 percent of women in these trials reported pelvic pain. By three months of treatment, this was reduced to a range of 9 to 28 percent, with those in the lower dose groups having lower or equivalent prevalence of pelvic pain.[35,36,57] Similar findings persisted at conclusion of 6 and 9 months of treatment. Once off treatment, prevalence of pelvic pain remained meaningfully lower with 6.3 to 37.0 percent of women affected at 9 months,[35,37] 16.2 to 18.6 percent at 12 months,[41] and 10 to 11 percent at 18 months.[37] The Rochester group reported change in pain using the McGill Pain Questionnaire and documented a steady decline from a high score of approximately 20 to about 6 points during the 6 months of treatment.[71]

Other Effects of Mifepristone Treatment

Improvements similar to those for pelvic pain were observed for other symptoms including pelvic pressure, urinary symptoms, lumbar pain, rectal pain, and dyspareunia assessed in the Cuban studies. In each case, the proportion with the symptom dropped by one to two-thirds or more and was sustained into followup with stability or a modest 2 to 6 percent increase in prevalence over the additional 9 to 18 months of followup. The Rochester group also reported that improvements in pelvic pressure, urinary frequency, low back pain, rectal pain, and pain with intercourse improved across treatment with active drug compared to placebo, with significant benefits for reducing pain with intercourse.[71]

Overall improvement in symptoms and physical well-being were also captured in this literature with the Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL) metrics. Composite scores improved,[35-37] as much as 50 of a possible 100 points (with placebo controls improving by 17 points).[71] Dose was not convincingly related to QOL scores.[35,37] Statistically significant improvements from baseline were noted in these aspects across studies at one or more doses:

- Symptoms[35,36,71]
- Concern[35,36,71]
- Activity[35,36]
- Inhibition/Self-consciousness[35,71]
- Control[35,36]
- Sexual function[35,71]
- Energy and mood[35,36]

This mirrored improvements in energy and fatigue, health status, and pain domains on Short Form 36 subscales.[71]

Risk of Harms from Mifepristone Treatment

No unanticipated adverse drug effects were identified in these trials. All trials conducted surveillance for the most serious known risk of harm, which is development of endometrial hyperplasia.

Selective progesterone receptor modulators are known to cause recognizable benign changes in the endometrium, designated progesterone modulator associated endometrial changes (PAEC).

To determine risk of hyperplasia, seven trials (eight publications) conducted an endometrial biopsy at an interim point or at the completion of treatment, unless the subject declined.[35-37,41,57,71,81,131] The percentage of subjects not undergoing at least one post-treatment biopsy were low in five studies,[37,41,57,71,81,131] 21 percent,[36] and 27 percent.[35]

Two placebo controlled studies with 5 mg mifepristone as the active intervention reported no hyperplasia in either group after 3[36] or 6[71] months of treatment. One study compared 5 mg to 2.5 mg mifepristone and reported no hyperplasia in either group after 3 months of treatment.[35] Four studies (reported in five publications) compared 10 mg to 5 mg mifepristone with treatment durations of 3 months,[57] 6 months,[41,81] 9 months,[37] and 12 months.[131] One study[81] reported an additional 6-month continuation, with a revised report of pathology at the 6-month time-point.[131]

Table 12 summarizes the number of women across the four studies who had biopsies with the indicated findings at specific time-points.[37,41,57,81,131] There were no reported cases of atypical hyperplasia. The counts of simple hyperplasia at 3 months of treatment were 2/92 (2%) for 5 mg dosage and 2/118 (2%) for 10 mg dosage. The counts of simple hyperplasia at 6 months of treatment were 1/81 (1%) for 5 mg dosage and 7/100 (7%) for 10 mg dosage. Data for 9 months and 12 months are sparse.

Table 12. Endometrial status with mifepristone treatment

Pathology Report	3 months*		6 months*		9 months		12 months	
	5 mg (3 studies)[37,41,57]	10 mg (3 studies)[37,41,57]	5 mg (3 studies†)[37,41,81,131]	10 mg (3 studies†)[37,41,81,131]	5 mg (1 study)[37]	10 mg (1 study)[37]	5 mg (1 study)[131]	10 mg (1 study)[131]
PAEC	14	32	22	39	5	11	0	0
Simple hyperplasia	2	2	1	7	0	0	0	1
Atypical hyperplasia ǂ	0	0	0	0	0	0	0	0
Other^	76	84	54	48	8	6	11	9
Total	92	118	81	100	13	17	11	10

Notes: *counts combined; † three studies reported in four publications; ^normal secretory or proliferative endometrium, other benign descriptor, or insufficient sample. ǂ Endometrial Intraepithelial Neoplasia has replaced atypical hyperplasia as the preferred term **Abbreviations:** mg=milligrams; PAEC: Benign progesterone modulator associated endometrial changes

All included trials also monitored liver function enzymes as elevations have been reported but not overt or sustained liver damage. The Cuban studies assessed asparate-aminotransferase (ASAT) and alanine-aminotransferase (ALAT) in five trials.[35-37,41,57] The percentages of women with elevated transaminases following mifepristone treatment ranged from 5.0 to 12.7 percent.

The maximum values when reported did not exceed 100 IU. Increases in hepatic enzymes were also noted in 8 percent of the women in one U.S. study[81] while no one in the other small U.S. study had abnormal liver function tests.[71] Abnormal liver enzyme was similar between the group treated with mifepristone (49/652, 7.5%) and the group who received placebo (5/67, 7.5%). There were no reports of any liver damage.

Nuisance bleeding in the form of irregular spotting and staining was common and is noted above.

Mifepristone Summary

Moderate evidence supports that mifepristone reduces size of fibroids and overall uterine volume. Heaviness of bleeding is reduced during treatment and measures of anemia improve. Information is unavailable to contribute to dose selection between higher and lower doses. Higher doses are inconsistently associated with greater reduction in size and faster resolution of symptoms but may also come with more nuisance bleeding. Since the medication is an oral daily agent, dose changes can be easily accomplished. Weak evidence suggests fibroids do resume growth after treatment; however, the majority of women can achieve symptomatic relief for a year or more after cessation of active treatment. Few participants in these trials pursued subsequent treatment during medical management or in the time after concluding active treatment suggesting, along with moderate strength of evidence for improvement in quality of life, that treatment with mifepristone can provide sufficient management of fibroid related symptoms.

Ulipristal acetate

Four trials, two conducted at National Institutes of Health[49,60] and two in research networks in Europe[26,31] have investigated use of ulipristal acetate as a treatment for fibroids with hope of demonstrating its utility for medical management to prevent or forestall surgery. The two earliest studies[49,60] followed participants to the end of 12 weeks of treatment with active drug. A third study treated for women for 12 weeks, waited until two normal menstrual cycles occurred and then treated women for an additional 12 weeks.[26] The fourth followed a similar protocol with up to four courses of 12 weeks[31] followed with a daily progestin (norethisterone acetate).

Effects of Ulipristal on Fibroid Characteristics

All four studies found ulipristal effective for reducing the size of individual fibroids and the overall fibroid burden as measured by total fibroid and uterine volume. A single course of 10 or 20 mg reduced fibroids size by 17 to 38 percent;[26,31,49,60] a repeated course of treatment reduced volume of the three largest fibroids by 54 to 58 percent from baseline to completion of both cycles.[31]

Effects of Ulipristal on Bleeding

Ulipristal, as intended, resulted in absent menses for the majority of women during treatment (range 62 to 100%) and the large majority reported improved bleeding.[26,49,60] This was also documented by improved or stable hematocrit or hemoglobin levels.[26,49,60] Cessation of bleeding at onset of treatment was prompt, ranging from a mean of 4 to 6 days.[26,31] Absence of bleeding was achieved more consistently with higher doses.[26,49]

Other Effects of Ulipristal

All ulipristal doses compared to placebo resulted in improved overall fibroid-related quality of life or subscale scores as measured by the UFS-QOL scale[26,49,60] though some time points lack statistical testing. Similar improvements were seen in the SF-36 scores.

Risk of Harms from Ulipristal

Treatment related effects were seen in ultrasounds and in some endometrial samples in all studies. Among a total of 399 biopsies, five cases of confirmed hyperplasia one with atypia was reported though not all participants were clearly accounted for in summaries of biopsies. The individual with simple atypical hyperplasia had spontaneous resolution in subsequent treatment cycles with no further intervention. Similar to mifepristone studies, modest elevations of liver function enzymes (AST/ALT <90 U/L) were seen during treatment; however no sustained elevations or evidence of liver damage were reported. Because ulipristal can theoretically influence adrenal function, two studies monitored for adrenal blockade with no evidence that any participants were affected.[49,60]

Ulipristal Summary

Moderate evidence supports that ulipristal reduces size of fibroids. Heaviness of bleeding is reduced with most women reporting absence of menses during treatment and measures of anemia stabilized or improved. Evidence is insufficient to contribute to dose selection between higher and lower doses and data on extended follow-up are lacking to gauge whether fibroids resume growth after treatment. . Use of a progestin for 10 days to prompt onset of menses shortened the time between treatment cycles in a single study.

Levonorgestrel Releasing Intrauterine Device / System (LNG-IUD / LNG-IUS)

We include one small, poor quality study that compared daily norethindrone acetate (NETA) with LNG-IUD for improving bleeding patterns among premenopausal women with uterine fibroids.[114] No placebo was used and women were not blind to intervention group.

Effects of LNG-IUD on Fibroid Characteristics

The study did not reported changes in fibroid volume.

Effects of LNG-IUD on Bleeding

Participants used a standardized pictorial method for reporting blood loss in a diary over the course of treatment. Visual blood loss scores improved by six months in both groups, with greater improvement in the IUD group which was reported to be statistically significant. Improvement in hemoglobin likewise occurred in both groups with a statistically greater improvement among those with an IUD.

Other Effects of LNG-IUD

Women with the LNG-IUD were more satisfied and more likely to continue treatment.

Risk of Harms from LNG-IUD

Risks of LNG-IUD / LNG-IUS have been addressed in separate literature.

LNG-IUD Summary

Based on the inclusion criteria for this review, evidence is insufficient for effects of LNG-IUS on bleeding, fibroid size, and quality of life. However, several systematic reviews have assessed the evidence for LNG-IUD / LNG-IUS management of uterine fibroids and uterine bleedings. This trial suggests local control of bleeding with an IUD can be successful even among women whose fibroid symptoms were considered appropriate for surgical intervention. However, the quality of the study was poor and thus evidence to guide care is insufficient.

Estrogen Receptor Agents

Three studies investigated the selective estrogen receptor modulator raloxifene in comparison to placebo.[80,86,91] Two were conducted in Italy by Palomba and colleagues with a total of 160 participants[86,91] and the third, a smaller study with 25 women in Austria.[80] Two studies focused on premenopausal women; one enrolled only post-menopausal women.[91] A single study[92] evaluated tamoxifen, which acts as an anti-estrogen within breast tissue and as an estrogen ligand in the endometrium.[139] We present them as a single grouping in this section (Table 13).

Raloxifene and Tamoxifen

Effects of Raloxifene and Tamoxifen on Fibroid Characteristics

Fibroid size decreased in two studies after three months of raloxifene or tamoxifen treatment.[80,91]

Table 13. Estrogen receptor agents and change in fibroid and uterine size

Author, Year	Daily Oral Dose	N	Rx Months	Fibroid Size Baseline; Followup(s) (cm^3)	Change	Uterine Size Baseline; Followup (cm^3)	Change
Jirecek S et al. (2004)[80]	180 mg raloxifene	13	3	59.0 ± 48.1 54.4 ± 47.9	↓4.4cm^3 p=0.03	NR	NR
Palomba S et al. (2002)[86]	60 mg raloxifene	29	0 3 6	51.7 ± 18.9 53.3 ± 19.7 57.4 ± 23.7	NR	203.9 ± 58.4 205.5 ± 58.3 209.5 ± 59.3	NR
Palomba S et al. (2002)[86]	180 mg raloxifene	30	0 3 6	47.4 ± 16.3 47.6 ± 18.1 47.7 ± 21.8	NR	206.7 ± 61.0 207.5 ± 62.3 207.5 ± 64.4	NR
Palomba S et al. (2001)[91]	60 mg raloxifene	31	12	127.1 ± 38.2 NR	↓27.0% p<0.05	295.5 ± 81.0 NR	↓40.0% p<0.05
Sadan O et al. (2001)[92]	20 mg tamoxifen	10	6	NR	NR	334 (130, 712)* NR	NR p=NS

Abbreviations: cm=centimeter; mg=milligrams; n=number; NR=Not reported; NS=Not significant

Effects of Estrogen Receptor Agents on Bleeding

In studies of raloxifene with premenopausal women, neither bleeding pattern[80,86,91] nor hemoglobin levels[86] improved compared to placebo, and a lower versus higher dose had similar results for days and severity of bleeding.[86] Among postmenopausal women, most women remained amenorrheic (83% in the raloxifene group and 86% in the placebo group at 9 months); the number of episodes of spotting and severity of bleeding were similar among women in the

treated and control group. Tamoxifen use in premenopausal women also did not influence length or severity of bleeding compared to placebo.[92]

Effects of Estrogen Receptor Agents on Other Symptoms

Only the tamoxifen comparison to placebo assessed pain; 70 percent of their participants had pain at enrollment. The treatment group reported significantly less pain by four months of treatment but not earlier.[92] No studies focused on improvement in other symptoms and none used quality of life measures.

Risk of Harms with Estrogen Receptor Agents

These studies reported no drug-related adverse events, and withdrawal from treatment for perceived side effects or adherence was rare and equal to placebo groups.[80,86,91] Simple ovarian cysts occurred in raloxifene treated women which resolved off medication.[80] Endometrial thickening occurs with tamoxifen and biopsies in this very small study were normal.[92]

Summary of Estrogen Receptor Agents

These agents were variably related to no or small decreases in fibroid size without improvement in bleeding. Some authors endorsed a focus on these medications because they are used for other indications and will be given to women with fibroids. These studies provide a low strength of evidence that raloxifene and tamoxifen are unlikely to prompt significant fibroid growth or to exacerbate bleeding if they are needed to treat women with fibroids for other conditions such as extended organ specific hormone suppression after breast cancer treatment.

Tranexamic Acid

We include one study, a pooled analysis of data from two independent trials of tranexamic acid treatment versus placebo for heavy uterine bleeding.[38] We did not include the primary studies that contributed data to the pooled analysis because those studies did not meet our review inclusion criteria because outcomes were reported for all women treated for heavy uterine bleeding and were not reported by fibroid status. The pooled analysis included a subset of women with uterine fibroids from each study. Women who received tranexamic acid reported statistically significant ($p<0.001$) reductions in menstrual blood loss at treatment cycle three compared with placebo.

Procedural Intervention: Overview

In this section we include studies of procedures to treat uterine fibroids including uterine artery occlusion and magnetic resonance guided focused ultrasound.

Uterine Artery Occlusion

Techniques to devascularize uterine fibroids include uterine artery embolization, coagulation, and occlusion. Most studies evaluated uterine artery embolization. A few uterine artery occlusion studies addressed bipolar coagulation of uterine vessels or other methods of severing the blood supply to fibroids. Laparoscopic occlusion of the uterine arteries involves a procedure to clip the uterine arteries at the level of the internal iliac artery. The collateral arteries between the uterus and the ovaries are also coagulated with bipolar forceps.

Uterine Artery Embolization (UAE)

Uterine artery embolization (UAE), also known as uterine fibroid embolization, uses particles to block the uterine artery blood supply to fibroids. The introduction of the particles occludes blood flow to the muscular portion of the uterus and causes infarction of the fibroids to control symptoms. This procedure is an option for women who wish to avoid surgery, are poor candidates for surgery or who wish to retain their uterus. The literature discussed in this section includes studies focusing on UAE only, with the exception of UAE compared with laparoscopic occlusion of the uterine arteries. Studies comparing UAE to surgery are discussed elsewhere.

High Intensity Focused Ultrasound (HIFU) and Magnetic Resonance-Guided Focused Ultrasound (MRgFUS)

High intensity focused ultrasound, guided by ultrasound or MRI, directs ultrasound energy (i.e., sound waves from the ultrasound) to the fibroid. This focused ultrasound beam induces thermal destruction of the target tissue. The treatment is conducted in an MRI suite using an imaging system that integrates real-time MRI and thermometry with an ultrasound unit specially designed to focus the ultrasound waves. This technique is relatively new, and few studies are available. In 2004, the FDA approved use of ExAblate System® MRgFUS system (InSightec Inc., Haifa, Israel) for ablation of uterine fibroid tissue in pre- or perimenopausal women with symptomatic uterine fibroids. Treatment is indicated for women with a uterine gestational size of less than 24 weeks. The FDA approved the ExAblate for two indications: treatment of uterine fibroids (leiomyomata) and palliation of pain associated with tumors metastatic to bone.

Since the prior review[17] which included findings from a prospective case series that was conducted to support an application for FDA approval of the magnetic resonance guided ultrasound system,[140,141] we identified five additional studies of HIFU.

Fibroid Ablation

Following feasibility studies that confirmed improvements in patient symptoms following radiofrequency volumetric thermal ablation of symptomatic fibroids, a multicenter study was conducted in the United States and Latin America to confirm sustained effects up to 36 months after treatment (ClinicalTrials.gov Identifier: NCT00874029). Investigators used the Acessa system (HaltMedical, Brentwood, CA, USA) for electrosurgical radiofrequency myoma ablation.[142-144]

Procedural Interventions: Results

We include 25 studies addressing uterine artery embolization, uterine artery occlusion, HIFU, and fibroid ablation.[25,27,29,30,32,33,39,42-44,47,48,51,52,61,62,69,70,73,76-79,82,90] Studies included 1979 women and were conducted in 15 different countries, most frequently in the United States (6 studies) or China (5 studies). Many of the studies (14 of 25)[25,30,33,42,43,48,51,62,70,73,76,79,82,90] of procedural interventions for uterine fibroids did not report source of funding. Three studies, two comparing embolic agents[27,47] and one that evaluated fibroid ablation,[29] were industry supported. Nine studies compared a procedural intervention to hysterectomy or myomectomy.[29,39,42,44,52,69,77,78,82] Studies were reported in 15 related publications[115-127,129,130] with outcomes reported at 24 months and up to 60 months after treatment.

Uterine Artery Occlusion

We identified 19 studies that randomized women to UAE, uterine artery coagulation, or uterine artery occlusion.[27,33,42-44,47,48,52,61,62,69,70,73,76-79,82,90] Uterine artery embolization is a vascular radiology procedure that introduces particles into the artery to block blood flow. Uterine artery coagulation and occlusion are done at the time of surgery to burn and occlude or suture and occlude vessels. Of these, eight studies compared an embolization agent to a different agent or different size;[27,33,43,47,48,62,76,79] seven studies compared UAE to surgery;[42,44,52,69,77,78,82] one compared UAE to a GnRH agonist (goserelin).[73] We identified three studies reported in four publications that assessed uterine artery occlusion. Two studies (reported in three publications) compared transcatheter[61] or laparoscopic[70,121] UAO to UAE; one compared laparoscopic bipolar coagulation alone to laparoscopic bipolar coagulation plus laparoscopic ligation of uterine nerves (LUNA) to determine if the addition of LUNA would improve postoperative pain and dysmenorrhea.[90] Much of the information on safety and long-term outcomes of uterine sparing, minimally invasive UAE is from two large trials (EMMY[78] and REST[69]). We assessed six studies as poor, five as good, and eight as moderate quality. The duration of followup ranged from 1 month to 24 months after treatment, with an average of 8.5 months. Frequently, the source of funding was not reported (11 studies).[33,42,43,48,62,70,73,76,79,82,90] Two studies of UAE with embolization particles were industry supported.[27,47]

Effects of Uterine Artery Occlusion on Fibroid Characteristics

Fibroid and uterine volume decreased significantly and consistently following UAE (up to 12 months post-procedure) regardless of the embolization agent or size of particles used to occlude the fibroid arteries. Additional longer-term followup reports from the EMMY trial confirm that fibroid and uterine volume reductions persist up to 5 years after UAE; however, the rate of subsequent treatment following UAE was high (Table 14 and Table 15).

Table 14. Uterine artery embolization and change in fibroid volume

Author, Year	UAE Description	Participants, N (Imaging Method)	Followup Time, months	Baseline; Followup (cm^3)	Change (cm^3 or percent)
Shlansky-Goldberg RD et al. (2014)[27]	UAE with SPVA particles	30 (MRI)	3	203.3 ± 275.1 104.2 ± 116.1	↓99.1 −76.9 ± 135.8%
Shlansky-Goldberg RD et al. (2014)[27]	UAE with TAG microspheres	30 (MRI)	3	141.1 ± 179.6 117.1 ± 179.5	↓24.0 −27.4 ± 42.3%
Song YG et al. (2013)[33]	UAE with gelatin sponge particles	30 (MRI)	3	265.3 ± 339.0 112.1 ± 167.4	↓153.2 NR
Song YG et al. (2013)[33]	UAE with nPVA particles	30 (MRI)	3	184.1 ± 141.3 97.2 ± 88.7	↓86.9 NR
Yu SC et al. (2011)[43]	UAE with PVA	30 (US)	9	197.7 ± 179 NR	NR −44.3 ± 52.4%
Yu SC et al. (2011)[43]	UAE with TAG microspheres	30 (US)	9	181.3 ± 140.0 NR	NR −55.0 ± 30.0%
Worthington-Kirsch RL et al. (2011)[47]	UAE with aPVA	22 (MRI)	6	130 ± 69 NR	NR[a]
Worthington-	UAE with TAG	24	6	96 ± 50	NR[a]

Author, Year	UAE Description	Participants, N (Imaging Method)	Followup Time, months	Baseline; Followup (cm^3)	Change (cm^3 or percent)
Kirsch RL et al. (2011)[47]	microspheres	(MRI)		NR	
Bilhim T et al. (2011)[48]	UAE with PVA particles, large	76 (MRI)	6	193.0 ± NR 98.0 ± NR	↓95.0 −49.2%
Bilhim T et al. (2011)[48]	UAE with PVA particles, small	77 (MRI)	6	210.0 ± NR 91.0 ± NR	↓119.0 −56.7%
Siskin GP et al. (2008)[62]	UAE with PVA microspheres	27 (MRI)	29 days post procedure	190.6 (0.4 to 670.6) 140.8 ± NR	↓49.8 −26.2%
Siskin GP et al. (2008)[62]	UAE with TAG microspheres	26 (MRI)	29 days post procedure	196.9 (14.1 to 536.6) 161.4 ± NR	↓35.5 −18.0%
Mara M et al. (2008)[124]	UAE	38 (MRI)	6	166.0 ± NR 69.0 ± NR	↓97.0 −58.7%
Vilos GA et al. (2006)[73]	UAE	10 (US)	12	257.3 ± 302.9 34.9 ± 42.4	↓222.4 −86.0%
Vilos GA et al. (2006)[73]	UAE plus goserelin	12 (US)	12	225.7 ± 182.9 94.7 ± 88.9	↓131.0 −58.0%
Spies JB et al. (2005)[76]	UAE with SPVA particles	17 (MRI)	3	142.4 ± 126.6 NR	↓29.6 ± 19.1 NR
Spies JB et al. (2005)[76]	UAE with TAG microspheres	19 (MRI)	3	150.1 ± 178.9 NR	↓39 ± 27 NR
Spies JB et al. (2004)[79]	UAE with TAG microspheres	54 (MRI)	3	138.4 ± 139.5 NR	NR −56.5 ± 22.2%
Spies JB et al. (2004)[79]	UAE with PVA particles	46 (MRI)	3	162.4 ± 169.3 NR	NR −42.5 ± 25.8%
Pinto I et al. (2003)[82]	UAE	38 (MRI and US)	6	84.4 (1.8 to 408) 45.5 (0.5 to 408)	↓38.9 −46.0%
Volkers et al. (2007)[127]	UAE	87 (US)	6 weeks	121.5 ± 150 70.5 ± 105†	NR −14.8%
Volkers et al. (2007)[127]	UAE	73 (US)	6	NR 54.4 ± 95	NR -42.1%
Volkers et al. (2007)[127]	UAE	66 (US)	12	NR 41.6 ±78	NR -54.5%
Volkers et al. (2007)[127]	UAE	62 (US)	24	NR 40.1 ± 87	NR -60.5%

Abbreviations: SPVA= spherical polyvinyl alcohol; TAGM= tris-acryl gelatin microspheres; UAE= uterine artery embolization; PVA= polyvinyl alcohol; TAG= tris-acryl gelatin; nPVA= non-spherical polyvinyl alcohol; US=ultrasound; MRI=magnetic resonance imaging. **Notes**: [a] data reported in figure only; †:n=72

Table 15. Uterine artery embolization and change in uterine volume

Author, Year	UAE Description	Participants, N (Imaging Method)	Followup Time, months	Baseline; Followup (cm^3)	Change (cm^3 or percent)
Shlansky-Goldberg RD et al. (2014)[27]	UAE with TAG microspheres	30 (MRI)	3	1491.6 ± 1456.5 909.1 ± 610.8	−557.8 ± 1101.1
Shlansky-Goldberg RD et al. (2014)[27]	UAE with SPVA particles	30 (MRI)	3	1536.7 ± 937.3 1058 ± 613.4	−436.4 ± 352.1
Song YG et al.	UAE with	30	3	960.27 ± 548.1	NR

Author, Year	UAE Description	Participants, N (Imaging Method)	Followup Time, months	Baseline; Followup (cm^3)	Change (cm^3 or percent)
(2013)[33]	gelatin sponge particles	(MRI)		498.61 ± 301.74	
Song YG et al. (2013)[33]	UAE with nPVA particles	30 (MRI)	3	934.47 ± 320.78 534.12 ± 193.67	NR
Yu SC et al. (2011)[43]	UAE with PVA	30 (NA)	NA	NR	NR
Yu SC et al. (2011)[43]	UAE with TAG microspheres	30 (NA)	NA	NR	NR
Worthington-Kirsch RL et al. (2011)[47]	UAE with TAG microspheres	24 (MRI)	6	650 ± 180 NR	NR[a]
Worthington-Kirsch RL et al. (2011)[47]	UAE with aPVA	22 (MRI)	6	540 ± 90 NR	NR[a]
Bilhim T et al. (2011)[48]	UAE with PVA particles, large	76 (MRI)	6	482 ± NR 266 ± NR	−44.8%
Bilhim T et al. (2011)[48]	UAE with PVA particles, small	77 (MRI)	6	515 ± NR 314 ± NR	−39.0%
Siskin GP et al. (2008)[62]	UAE with PVA microspheres	27 (MRI)	29 days post procedure	564 ± NR 470.7 ± NR	−16.5%
Siskin GP et al. (2008)[62]	UAE with TAG microspheres	26 (MRI)	29 days post procedure	611.6 ± NR 534.3 ± NR	−12.6%
Mara M et al. (2008)[124]	UAE	38 (NA)	NA	NR	NR
Vilos GA et al. (2006)[73]	UAE	10 (US)	12	476.6 ± 279.3 200.6 ± 74.1	−58.0%
Vilos GA et al. (2006)[73]	UAE plus goserelin	12 (US)	12	556.4 ± 271.8 305.1 ± 141.3	−45.0%
Spies JB et al. (2005)[76]	UAE with SPVA particles	17 (MRI)	3	510.5 ± 314.8 NR	−16.4 ± 23.5%
Spies JB et al. (2005)[76]	UAE with TAG microspheres	19 (MRI)	3	618.9 ± 305.1 NR	−27.4 ± 22.4%
Spies JB et al. (2004)[79]	UAE with PVA particles	46 (MRI)	3	603.9 ± 343.3 NR	−30.2 ± 17.3%
Spies JB et al. (2004)[79]	UAE with TAG microspheres	54 (MRI)	3	648.7 ± 326.7 NR	−35.1 ± 16.7%
Pinto I et al. (2003)[82]	UAE	38 (NA)	NA	NR	NR
Volkers et al. (2007)[127]	UAE	87 (US)	6 weeks	471.9 ± 450 268 ± 209[†]	NR −20.9%
Volkers et al. (2007)[127]	UAE	66 (US)	6	NR 235.3 ± 204	NR −30.9%
Volkers et al. (2007)[127]	UAE	62 (US)	12	NR 201.2 ±198	NR −44.3%
Volkers et al. (2007)[127]	UAE	62 (US)	24	NR 170.2 ± 135	NR −48.2%
Ananthakrishnan et al. (2013)[117]	UAE	85 (MRI)	6	670 ± 503 422 ± 353[*]	NR −34.0%
Ananthakrishnan	UAE	68	60	NR	NR

Author, Year	UAE Description	Participants, N (Imaging Method)	Followup Time, months	Baseline; Followup (cm^3)	Change (cm^3 or percent)
et al. (2013)[117]		(MRI)		292 ± 287	−53.0%

Abbreviations: SPVA= spherical polyvinyl alcohol; TAGM= tris-acryl gelatin microspheres; UAE= uterine artery embolization; PVA= polyvinyl alcohol; TAG= tris-acryl gelatin; nPVA= non spherical polyvinyl alcohol; US=ultrasound; MRI=magnetic resonance imaging; NR=not reported; NA=not applicable; **Notes**: uterine volume not reported in the following: Yu SC et al. (2011);[43] Mara M et al. (2008);[124] Pinto I et al. (2003);[82] *n=84; †n=69

Effects of Uterine Artery Occlusion on Bleeding

Changes in bleeding were reported as incidence of amenorrhea, change in bleeding score using a scale from −5 to +5, and rate of self-reported dysmenorrhea or menorrhagia (Table 16).

Table 16. Bleeding outcome (continuous) in uterine artery occlusion

Citation	Group Participants, N	Outcome	Followup Time, months	Baseline Followup	Change
Song YG et al. (2013)[33]	UAE with gelatin sponge particles	Bleeding Questionnaire[2]	0 3	8.1 ± NR 2.0 ± NR	NR
Song YG et al. (2013)[33]	UAE with nPVA	Bleeding Questionnaire[3]	0 3	7.9 ± NR 2.5 ± NR	NR
Spies JB et al. (2004)[79]	UAE with PVA	Bleeding Questionnaire[4]	3	NR	↑3.3 ± 1.5
Spies JB et al. (2004)[79]	UAE with TAG microspheres	Bleeding Questionnaire[5]	3	NR	↑3.2 ± 1.9
Spies JB et al. (2005)[76]	UAE with SPA	Bleeding Questionnaire[6]	0 3	NR 3.1 ± 1.7	NR
Spies JB et al. (2005)[76]	UAE with TAG microspheres	Bleeding Questionnaire[7]	0 3	NR 4.0 ± 1.4	NR
Ruuskanen A et al. (2010)[52]	UAE	Duration of menstrual flow, days	0 24	4.9 ± 2.4 3.3 ± 4.4	↓1.6
Rashid et al. (2010)[120]	UAE	Duration of menstrual flow, days	6 12	NR NR	↓1.4 ± 3.7 ↓1.7± 3.8
Song YG et al. (2013)[33]	UAE with gelatin sponge particles	Dysmenorrhea Questionnaire[8]	0 3	7.6 ± NR 2.0 ± NR	NR
Song YG et al. (2013)[33]	UAE with nPVA	Dysmenorrhea Questionnaire[9]	0 3	7.7 ± NR 2.3 ± NR	NR
Cunningham E et al. (2008)[61]	UAE	Bleeding, mean change in AMSS	3	NR	−58.0%
Cunningham E et al. (2008)[61]	TUAO	Bleeding, mean change in AMSS	3	NR	−63.0%
Rashid et al. (2010)[120]	UAE	Menstrual cycle length, days	6	NR	−0.3 ± 3.8
Rashid et al.	UAE	Menstrual cycle	12	NR	0.7 ± 4.9

[2] Questionnaire range from 0 (no impact) to 10 (severe impact)
[3] Questionnaire range from 0 (no impact) to 10 (severe impact)
[4] 11-point questionnaire range -5 to +5
[5] 11-point questionnaire range -5 to +5
[6] 11-point questionnaire range -5 to +5
[7] 11-point questionnaire range -5 to +5
[8] Questionnaire range from 0 (no impact) to 10 (severe impact)
[9] Questionnaire range from 0 (no impact) to 10 (severe impact)

Citation	Group Participants, N	Outcome	Followup Time, months	Baseline Followup	Change
(2010)[120]		length, days			
Ruuskanen A et al. (2010)[52]	UAE	Hemoglobin, g/L	0 24	131.4 ±13.9[a] NR	↑9.5 ±13.9[a] p=NR
Volkers et al. (2007)[127]	UAE	Hemoglobin, g/dL	24	NR	↑1.37
Volkers et al. (2007)[127]	UAE	**Duration of heavy menstruation, days**	0	3 (1-28), n=88	NR
			1.5	2 (0-14), n=81	NR
			6	2 (0-7), n=80	NR
			12	1 (0-10), n=81	NR
			24	0 (0-6), n=81	NR

Abbreviations: UAE=uterine artery embolization; NR=not reported; g/dL=grams per deciliter; AMSS=Aberdeen Menorrhagia Symptom Scale

Effects of Uterine Artery Occlusion on Fibroid-Related Pain

Most women who underwent LBCUV reported slight, significant, or complete improvement in dysmenorrhea symptoms at six months after procedure (92.1% who received LBCUV plus LUNA and 76.2% of women who were treated by LBCUV alone). At baseline, 73 women (90.1%) in the UAE arm of the EMMY trial complained of lower abdominal pain. At 24 months of follow-up, 84.9 percent of women reported moderate improvement of pain.[127] In another study, nine of the 27 women (33%) in the UAE arm reported dysmenorrhea at baseline while only four (15%) complained of dysmenorrhea at the 2 year follow-up, thus showing a reduction of 56 percent from baseline.[52]

Other Treatment Effects of Uterine Artery Occlusion

Quality of Life

Overall improvement in symptoms and physical well-being were reported using the UFS-QOL, SF-36, and EQ-5D™. Quality of life was not reported following laparoscopic or transcatheter uterine artery occlusion[61,70,121] or following bipolar coagulation of uterine vessels.[90]

Quality of Life: UFS-QOL

Significant improvement in symptoms was reported by the UFS-QOL in a small study (n=36).[76] The study by Shlansky-Goldberg et al. (2014)[27] reported changes in symptom and subscores on the UFS-QOL in figures only. Changes in the total quality of life score were reported in figures only in another small study (n=44) comparing UAE with TAG microspheres to UAE with polyvinyl alcohol particles.[47] Total quality of life scores improved at 3 months after uterine artery embolism in both groups (UAE with TAG microspheres: 36.0 ± 25.5 and UAE with polyvinyl alcohol particles: 23.1 ± 23.4, p values not reported).[79] A 2012 study was powered to detect a 10-point difference in quality of life outcomes among premenopausal women with symptomatic fibroids following abdominal myomectomy or UAE.[44] Authors reported significant improvements from baseline in overall quality of life and severity scores after UAE (p=NR).[44]

Quality of Life: SF-36

Three trials (Jun F et al. at 6 months,[42] the REST[69] and EMMY trials up to 60 months[123]) reported SF-36 quality of life outcome measures (Table 17). At 6 months, the 2012[42] trial

observed a significant improvement in QOL scores from baseline (p=NR) while the REST trial[118] reported a gain in QOL after UAE with 5-year SF-36 scores being comparable to normative data. The EMMY trial[123] also found within the UAE group, all general health-related quality of life improved at 6 months and afterwards when compared to baseline values ($p<0.05$). Using the Body Image Scale, the EMMY trial[125] reported that body image improved significantly from baseline ($p<0.05$) in the UAE group at 6 (−1.34), 18 (−1.24) and 24 (−1.06) months with lower scores representing favorable body image and negative numbers indicating improvement.

Table 17. Quality of life reported by SF-36 following UAE

Trial	Outcome	Outcome details	Followup (months)	Baseline Score, mean (SD)	Followup Score, mean (SD)
Jun F et al. (2012)[42]	Quality of life (SF-36)	Physical function Social function Mental health Emotional role Vitality	6	57.7 ± 17.0 44.6 ± 7.0 43.3 ± 22.1 50.0 ± 24.9 54.0 ± 11.5	68.4 ± 6.1 63.0 ± 10.2 71.9 ± 6.2 69.6 ± 6.7 66.2 ± 6.0
Moss JG et al. (2011)[118] Rashid S et al. (2010)[120] Edwards RD et al. (2007)[69]	Quality of life (SF-36)	Physical function Social function Mental health Emotional role Vitality Physical role Bodily pain General health	12	82 ± 19 63 ± 27 63 ± 18 60 ± 43 41 ± 22 51 ± 41 52 ± 22 61 ± 19	92 ± 14 84 ± 23 76 ± 17 81 ± 35 62 ± 21 76 ± 40 76 ± 23 74 ± 20
Hehenkamp WJ et al. (2008)[123]	Quality of life change score from baseline	SF36-MCS	12 24 60	NR NR NR	6.3 ($p<0.05$) 5.8 ($p<0.05$) 6.3 ($p<0.05$)
Hehenkamp WJ et al. (2008)[123]	Quality of life change score from baseline	SF36-PCS	12 24 60	NR NR NR	7.3 ($p<0.05$) 9.4 ($p<0.05$) 8.5 ($p<0.05$)
Hehenkamp WJ et al. (2007)[125]	Body Image	Body image Scale (0-30)	6 18 24	NR NR NR	Improvement (−1.3) Improvement (−1.2) Improvement (−1.1) All $p<0.05$

Abbreviations: BL=baseline; SF-36=Medical Outcomes Study 36 –Item Short Form General Health Survey; n=number; NR=not reported; SD=standard deviation

Quality of Life: EQ-5D™

The REST trial did not report the change in EQ-5D™ or symptom status score from baseline at 12 months or at 5 years, though the absolute scores showed improvement (Table 18)**.** Significant improvements ($p<0.05$) from baseline in EQ-5D™ scores were observed at 6 months and afterwards in the EMMY trial.[123]

Table 18. Quality of life reported by EQ-5D™ following UAE

Author, Year	Outcome Details	Followup, months	Baseline Score, mean (SD)	Followup Score, mean (SD)
Edwards RD et al. (2007)[69] and Moss JG et al. (2011)[118]	EQ-5D™ total score (0 to 100)	12 60	70.0 ± 16.0 NR	82.0 ± 16.0 85.0 ± 13.0
Edwards RD et al. (2007)[69] and Moss JG et al. (2011)[118]	EQ-5D™ symptom status score	12 60	NR NR	3.6 ± 2.0 4.5 ± 0.1
Hehenkamp WJ et al. (2008)[123]	EQ-5D™ change from	24	NA	0.086

baseline score	

Abbreviations: EQ-5D=EuroQol-5D questionnaire; n=number; NR=not reported; SD=standard deviation

Satisfaction

Out of the seven studies comparing UAE with surgeries, satisfaction rates were reported in all except one study (FUME trial[44]). Satisfaction with outcome was measured by asking women if she would undergo the same treatment again,[82] if she obtained symptom relief,[77,124] satisfaction with the treatment,[52,119] or if she would recommend treatment to a friend.[42,69,119] One trial also reported satisfaction rate without providing details of the criteria.[42] Satisfaction rates (Table 19) ranged from 78 to 89 percent at 6 months[82,124] to 82 to 88 percent at 1 year[42,69] to about 90 percent at 2 years.[52,119] Satisfaction rates remained high (84% to 90%) at 5-year followup.[118,119]

Table 19. Patient satisfaction following UAE for fibroid treatment

Study	Measure	Followup, months	Rate
Pinto I et al. (2003)[82]	Would undergo same treatment again	6	28/36 (78.0)
Mara M et al. (2008)[124]	Symptom relief	6	46/52 (88.5)
Edwards RD et al. (2007)[69]	Would recommend to a friend	12	84/95 (88.0)
Jun F et al. (2012)[42]	Would recommend to a friend	12	51/62 (82.0)
Jun F et al. (2012)[42]	Satisfactory rate	12	52/62 (84.0)
van der Kooij SM et al. (2010)[119]	Satisfaction with outcome	12	68/81 (84.0)
van der Kooij SM et al. (2010)[119]	Satisfaction with outcome	24	74/81 (91.4)
Ruuskanen A et al. (2010)[52]	Would choose treatment again	24	24/27 (89.0)
Moss JG et al. (2011)[118]	Would recommend to a friend	60	84/93 (90.0)
van der Kooij SM et al. (2010)[119]	Satisfaction with outcome	60	68/81 (84.0)
van der Kooij SM et al. (2010)[119]	Would recommend to a friend	60	61/79 (77.2)

Recurrence and Subsequent Treatment

Two studies[117,145] reported fibroid recurrence (Table 20). In one trial, women were followed for a mean period of 26 months after UAE.[145] By 2 years, there were six women (10.3%) with regrowth or recurrence of fibroids.[145] The REST trial reported fibroid recurrence in 5 out of 68 women (7%) 5 years after UAE treatment.[117]

Table 20. Fibroid recurrence rate following UAE for fibroid treatment

Author, Year	Outcome	Followup, months	Rate
Mara M et al. (2008)[124]	Fibroid recurrence	6	6/58 (10.3)
Ananthakrishnan G et al. (2013)[117]	New fibroid formation	6	1/97 (1.0)
Ananthakrishnan G et al. (2013)[117]	New fibroid formation	60	5/68 (7.0)

Subsequent treatment was reported in seven trials with length of followup ranging from six to 60 months (Table 21). Hysterectomy was the most frequent intervention (17.5%) followed by myomectomy (8.8%), repeat embolization (6.3%), IUD (8%), medication (6.7%) and endometrial ablation (1.2%).[42,44,52,82,118,119,124]

Table 21. Subsequent treatment for uterine fibroids following UAE

Author, Year	Baseline, N	Followup, months	Followup, N	HYS	MYO	UAE	ABL	MED / IUD	No Rx	Rate
Mara M et al. (2008)[124]	58	24	58	0	19	0	0	0	39	19/58 (32.8)
Manyonda IT et al. (2012)[44]	82	12-24	63	6	2	1	0	0	54	9/63 (14.3)
Moss JG et al. (2011)[118]	106	By 60	96	18	0	8	0	0	69	27/96 (28.1)
Jun F et al. (2012)[42]	63	6-12	62	0	1	5	0	0	56	6/62 (9.7)
van der Kooij SM et al. (2010)[119]	88	By 60	75	23	2	0	1	7	37	38/75 (50.7)
Pinto I et al. (2003)[82]	38	6	37	2	0	0	0	0	35	2/37 (5.4)
Ruuskanen A et al. (2010)[52]	27	24	26	3	1	0	0	1	21	5/26 (19.2)

Abbreviations: HYS= hysterectomy; MYO=myomectomy; UAE=uterine artery embolization; MED/IUD=medication or intrauterine device; N= number; No Rx=no treatment

Effects of Uterine Artery Occlusion on Pregnancy Outcomes

Pregnancy outcomes were not reported following laparoscopic or transcatheter uterine artery occlusion[61,70,121] or following bipolar coagulation of uterine vessels (Table 22).[90] Ovarian failure, measured by follicle stimulating hormone (FSH) >40 IU/L and anti-Mullerian hormone (AMH), was reported in two trials (REST and EMMY).[120,126] In the trial involving 88 women after UAE, FSH increased significantly compared to baseline (+12.1, p=0.001) after 24 months of treatment with UAE. FSH >40 IU/L was reported in 12 percent and 18 percent at 12 and 24 months, respectively.[126] The changes in FSH scores at 6 weeks and 12 months from baseline were also significant (p<0.05) after UAE.

A similar proportion of women (11%) were observed to have FSH>40 IU/L at 12 months after UAE in another trial.[120] Levels of AMH were significantly lower (p<0.05) from baseline values at each followup up to 24 months after UAE suggesting that UAE might be more harmful to ovarian reserve.[126] An elevation of FSH greater than 10 IU/L was reported in 8 of 58 women (14%) in another trial at 6 months.[124]

The trial by Mara et al.[124] was the only study that prespecified pregnancy and live birth as outcomes of interest. By 2 years of followup, there were 13 pregnancies (50%) and five live births (19.2%) reported out of those women wanting to conceive. The REST trial[69] did not prespecify pregnancy outcomes, but did report seven pregnancies after UAE at 12 months. The EMMY trial[127] reported one unplanned pregnancy after UAE at 24 months in a 39-year-old multipara, who delivered a healthy child after secondary cesarean section for fetal distress.

Table 22. Pregnancy and fertility status reported in studies of UAE for fibroid treatment

Author, Year	Measure	Followup, months	Rate or Mean (SD)
Hehenkamp WJ et al. (2007)[126]	FSH >40 IU/L	1.4	10/79 (13.0)
		6	7/78 (9.0)
		12	9/74 (12.0)

Author, Year	Measure	Followup, months	Rate or Mean (SD)
		24	14/80 (18.0)
Rashid S et al. (2010)[120]	FSH>40IU/L	12	7/62 (11.0)
Mara M et al. (2008)[124]	FSH>10 IU/L	6	8/58 (13.8)
Hehenkamp WJ et al. (2007)[126]	AMH (mean change score)	1.4	−0.62
		6	−0.23
		12	−0.31
		24	−0.42
Edwards RD et al. (2007)[69]	Pregnancy	12	7/95 (7.4)
Volkers NA et al. (2007)[127]	Pregnancy	24	1/81 (1.2)
Mara M et al. (2008)[124]	Pregnancy	24	13/26 (50.0)
Mara M et al. (2008)[124]	Live birth	24	5/26 (19.2)

Abbreviations: BL= baseline; AMH= anti-Muellerian hormone; FSH= follicle stimulating hormone; NS= not significant; SD= standard deviation

Potential Harms of Uterine Artery Occlusion

Transfusion

Three studies of UAE compared to myomectomy or hysterectomy reported incidence of transfusion.[78,82,124] None of the 186 patients required transfusion after the UAE procedure.

Other Major Complications

The rate of major complications, including unplanned hysterectomy, re-hospitalization, ovarian failure, and pulmonary embolism during and following UAE ranged from 1.2 to 6.9 percent periprocedurally, up to 3 percent by 1 year,[44] and about 5 percent at 2 years (Table 23).[122] The rates of major complications were highest in two studies that reported long-term followup (21% at 5 years in the REST trial[118] and 16.8% at 32 months in a second study[69]).

Table 23. Major complication rates reported in studies of UAE

Author, Year	Timepoint	Rate
Mara M et al. (2008)[124]	Periprocedural	4/58 (6.9)[a]
Pinto I et al. (2003)[82]	Intraprocedure	0/40 (0)
Pinto I et al. (2003)[82]	Postprocedure	1/40 (2.5)
Hehenkamp WJ et al. (2005)[78]	In the hospital	1/81 (1.2)
Hehenkamp WJ et al. (2005)[78]	6 weeks	3/81 (3.7)
Mara M et al. (2008)[124]	6 months	0/58 (0)
Jun F et al. (2012)[42]	6 months	0 (0)
Mara M et al. (2008)[124]	1 year	0/58 (0)
Manyonda IT et al. (2012)[44]	1 year	2/63 (2.9)
Ruuskanen A et al. (2010)[52]	2 years	0 (0)
Volkers NA et al. (2008)[122]	2 years	4/81 (4.9)
Edwards RD et al. (2007)[69]	32 months	16/95 (16.8)
Moss JG et al. (2011)[118]	By 5 years	20/96 (21.0)

Notes: [a] included one artery dissection and 3 serious events;

Complication rates were often low in the studies comparing embolic agents[33,43,48,62,79] (Table 24), however the duration of followup among these studies was nine months or less.

Table 24. Harms reported in uterine artery occlusion arms (6 studies)

Author, Year	Arm	N	Adverse Event	Rate
Bilhim T et al. (2011)[48]	UAE with small PVA particles	80	Major complications- readmission to hospital fibroid expulsion	2/80 (2.5)
Bilhim T et al. (2011)[48]	UAE with large PVA particles	80	Major complications- readmission to hospital fibroid expulsion	1/80 (1.3)
Hald K et al. (2007)[70]	Laparoscopic uterine artery occlusion	29	Buttock claudication; fibroid expulsion; pulmonary embolism	3/29 (10.3)
Siskin GP et al. (2008)[62]	UAE with TAG microspheres	26	Unplanned hysterectomy	0/26 (0)
Siskin GP et al. (2008)[62]	UAE with PVA microspheres	27	Unplanned hysterectomy	1/27 (3.7)
Song YG et al. (2013)[33]	UAE with nPVA	30	Major complication (not specified)	0/30 (0)
Song YG et al. (2013)[33]	UAE with gelatin sponge particles	30	Major complication (not specified)	0/30 (0)
Spies JB et al. (2004)[79]	UAE with TAG microspheres	54	Pulmonary embolism	1/54 (1.9)
Spies JB et al. (2004)[79]	UAE with PVA	46	Pulmonary embolism	0/46 (0)
Yu SC et al. (2011)[43]	UAE with TAG microspheres	30	Major complications Premature ovarian failure	0/30 (0) 2/27 (7.0)
Yu SC et al. (2011)[43]	UAE with PVA	30	Major complications Premature ovarian failure	2/30 (6.7) 3/29 (11.0)

Abbreviations: UAE: uterine artery embolization; Notes: Seven studies did not report harms: Cunningham E et al. (2008);[61] Shlansky-Goldberg RD et al. (2014);[27] Spies JB et al. (2005);[76] Spies JB et al. (2005);[76] Vilos GA et al. (2006);[73] Worthington-Kirsch RL et al. (2011);[47] Yen YK et al. (2001).[90]

Summary of Uterine Artery Occlusion

There was high strength of evidence that uterine artery occlusion was effective in fibroid volume reduction though only low strength of evidence for improvements in bleeding symptoms. There is moderate strength of evidence that quality of life is improved following embolization. Occlusion does allow women to preserve future fertility. Five-year followup data was available from two large good and fair quality trials that well over half women who received an embolization did not need a subsequent intervention including subsequent hysterectomy.

HIFU and MRgFUS

We identified five studies,[25,30,32,39,51] reported in six publications,[25,30,32,39,51,115] assessing high intensity focused ultrasound (HIFU) as treatment for uterine fibroids. Interventions included HIFU (2 studies reported in 3 publications),[39,51,115] HIFU plus contrast enhanced ultrasound (1 study),[25] HIFU plus intratumoral ethanol injection (1 study)[30] and HIFU plus SonoVue (1 study).[32] Studies were published between 2010 and 2015. All but one small study conducted in Italy in 2015[25] were carried out in China.[30,32,39,51] These studies included 363 participants. The smallest study[25] included 33 women and the largest RCT[39] included 110 women with uterine fibroids. We assessed all as poor quality.

Effects of MRgFUS on Fibroid Characteristics

Three studies reported fibroid volume following focused ultrasound destruction of fibroids (Table 25).[25,30,32] The magnitude of fibroid volume reduction was greater at 12 months[25] after ultrasound destruction than at 1 month post-treatment.[30]

Table 25. Ultrasound destruction and change in uterine fibroid volume

Author, Year	Arm Description	N	Followup	Baseline; Followup (cm^3)	Change (cm^3)
Jiang N et al. (2014)[32]	HIFU	40	postprocedure	NR 82.6 ± 102.0	NR
Jiang N et al. (2014)[32]	HIFU plus SonoVue	40	postprocedure	NR 58.6 ± 69.3	NR
Orsi F et al. (2015)[25]	HIFU	17	12 months after procedure	189.6 ± 190.0 100.0 ± 144.0	↓89.9 −47.2%
Orsi F et al. (2015)[25]	HIFU plus CEUS	20	12 months after procedure	419.2 ± 409.0 249.3 ± 257.0	↓169.9 −40.5%
Yang Z et al. (2014)[30]	HIFU	20	1 month after procedure	156.2 ± 130.1 108.3 ± 926.1	↓47.9
Yang Z et al. (2014)[30]	HIFU plus USg intramural ethanol injection	20	1 month after procedure	157.7 ± 198.5 112.8 ± 145.2	↓44.9

Notes: Table does not include two studies of HIFU (Wang X et al. (2013)[39] and Meng X et al. (2010)[51] that did not report fibroid volume. **Abbreviations:** HIFU= high intensity focused ultrasound; CEUS= contrast enhanced ultrasound; USg= ultrasound guided; NR= not reported; ND= no data

Effects of MRgFUS on Bleeding and Fibroid Related-Pain

Not reported.

Other Treatment Effects of MRgFUS

One month after HIFU, the mean change (baseline not reported) in UFS-QOL score was 16 or more points among 37 patients; however, four patients experienced persistent symptoms and underwent a second HIFU procedure.[25] A study that compared myomectomy to HIFU reported treatment effects on sexual function at 6 months after procedure among 100 women. The total sexual function score using the brief index of sexual function for women (BISF-W) improved significantly ($p<0.05$) from 24.6 ± 6.6 at baseline to 26.7 ± 5.2 at 6 months in the HIFU group (n=48).[25]

Effects of MRgFUS on Pregnancy Outcomes

No study of HIFU treatment for uterine fibroids reported pregnancy outcomes. All included women of reproductive age. One study required that eligible patient have no desire to conceive and a second study required that enrolled women not have plans to become pregnant within two months of treatment.

Potential Harms of MRgFUS

No major harms were observed postprocedure in the 211 patients who received HIFU for fibroid treatment.[25,30,32,39,51] One study reported on transfusion following HIFU with none of the 48 women who received treatment requiring transfusion.[39]

MRgFUS Summary

Studies of HIFU reported few outcomes. These studies reported intra and post procedural outcomes, specifically technical success and safety of the technique. With the exception of one study that assessed sexual function, publications did not assess symptoms or long-term outcomes

Fibroid Ablation

We included two studies that assessed outcomes of fibroid ablation for management of uterine fibroids. One, a postmarket study sponsored by Halt Medical and published in 2014 evaluated radiofrequency volumetric ablation (n=26[10]) compared with myomectomy (n=25).[29] A second, larger study published in 2010 randomized women to thermal ablation (n=50) (Valleylab Cool-Tip™ RF Ablation System, Valleylab/Tyco Healthcare Group, Boulder, CO, USA) or HIFU (n=50).[51] These studies were conducted in Germany[29] and China[51] and included 75 patients. Both were assessed as poor quality.

Effects of Fibroid Ablation on Fibroid Characteristics

The efficacy of the procedure, reported as fibroids excised or ablation rate was similar. In the smaller study, author reported that radiofrequency volumetric ablation successfully excised 98.6 percent (71 of 72) fibroids in 25 patients.[29] The larger study reported ablation rates of 86 percent (by volume) and 90 percent (by diameter) following radiofrequency ablation to treat uterine fibroids among 50 women.[51]

Effects of Fibroid Ablation on Bleeding

These studies of fibroid ablation did not report fibroid-related bleeding.

Effects of Fibroid Ablation on Fibroid-Related Pain

These studies of fibroid ablation did not report fibroid-related pain.

Potential Harms of Fibroid Ablation

With the exception of one case of rehospitalization for unexplained vertigo after treatment,[29] authors reported no major complications following radiofrequency ablation treatment.[51]

Fibroid Ablation Summary

We identified two small studies, both assessed as poor quality, that evaluated thermal or radiofrequency ablation techniques for fibroid removal. Similar to the studies of HIFU, these studies focused on technical success and safety of the technique and did not address symptoms or long-term outcomes. However, the authors of a 2014 post market study publication note that study investigators will follow patients for 5 years to obtain pregnancy and satisfaction outcomes.

[10] 26 allocated, 25 received treatment (procedure was terminated in OR in 1 patient)

Surgical Intervention: Overview

Endometrial Ablation

Endometrial ablation is a procedure that destroys (ablates) the uterine lining (endometrium) using one of these techniques: laser thermal ablation, radiofrequency thermal ablation, thermal balloon ablation, saline and electricity, freezing, or microwaves. The goal of endometrial ablation is to reduce or eliminate uterine bleeding. Pregnancy is not recommended after endometrial ablation, and often tubal occlusion is performed as part of the procedure. A submucosal fibroid can be resected by hysteroscopy, as a preliminary part of the endometrial ablation procedure.

Myomectomy

Myomectomy is intended to excise the fibroid(s) that can be surgically removed, followed by repairs of the defect in the uterine wall. The intention of myomectomy is to preserve the uterus. For this reason, myomectomy is a surgical option available to women who wish to be able to have future pregnancies or who wish to retain their uterus. During the years that follow myomectomy, the possibility of new fibroid growth or fibroid recurrence exists and this could lead to subsequent intervention(s).[146] Myomectomy procedures could be completed with or without a morcellator. Myomectomy procedures could be combined with temporary or permanent uterine artery occlusion.

Hysterectomy

Hysterectomy is a standard treatment for symptomatic fibroids in women who have completed childbearing. Hysterectomy is the surgical removal of the uterus. Hysterectomy does not require salpingo-oophorectomy (surgical removal of the fallopian tubes and ovaries) but surgical removal of these organs may be done concurrently. Surgery that removes the entire uterus and cervix as well as the ovaries is properly called total hysterectomy with bilateral salpingo-oophorectomy. Surgery that leaves the uterine cervix intact is called “supracervical” or “subtotal”. The surgical approach may be through an open incision (laparotomy) or with the use of a laparoscope (laparoscopic). The open incision may be reduced in size (minilaparotomy). The laparoscopic procedure may be exclusive (total laparoscopic hysterectomy), or may include a vaginal procedure (laparoscopic assisted vaginal hysterectomy).

Hysterectomy procedures could be completed with or without a morcellator.

Surgical Interventions: Results

We identified 36 studies[28,29,34,39,40,42,44-46,50,52,54,55,58,59,64,66,69,72,74,75,77,78,82-84,88,89,93-95,97,98,100,104,110] evaluating a surgical intervention to treat women with uterine fibroids. Studies were conducted in six countries (Brazil, China, France, Germany, Italy, and Taiwan) and randomized 3,080 women with uterine fibroids to hysterectomy or myomectomy. We assessed study quality as good in nine studies,[28,45,55,58,59,64,78,83,84] fair in 11 studies,[44,66,69,77,82,93-95,97,98,104] and poor in 16 studies.[29,34,39,40,42,46,50,52,54,72,74,75,88,89,100,110]

Endometrial Ablation

We identified one study of endometrial ablation.[95] This fair quality study reported amenorrhea, bleeding, hemoglobin, patient satisfaction and the incidence of harms in patients treated by endometrial ablation (n=54) or endometrial thermal ablation (n=42).

Effects of Endometrial Ablation on Fibroid Characteristics

Not reported.

Effects of Endometrial Ablation on Bleeding

Menorrhagia, reported by the pictorial blood loss chart, decreased significantly ($p<0.0001$) in both groups from baseline to 12 month after procedure. This patient-reported outcome of improved bleeding symptoms was confirmed by a clinically significant increase in mean hemoglobin in both groups ($p<0.001$) (Table 26).[95]

Table 26. Endometrial ablation and changes in hemoglobin

Author, Year	Arm Description	N	Followup	Baseline; Followup (g/dl)	Change (g/dl)
Soysal ME et al. (2001)[95]	Ablation, endometrial roller ball	54	12 months after procedure	9.8 ± 1.2 12.9 ± 0.9	↑3.0 ± 1.6 p<0.0001
Soysal ME et al. (2001)[95]	Ablation, endometrial thermal balloon	42	12 months after procedure	10.0 ± 1.5 12.8 ± 0.9	↑2.7 ± 1.9 p<0.0001

Abbreviations: N=number of participants; g/dl=grams per deciliter

Other Treatment Effects of Endometrial Ablation

The rate of reintervention was similar following roller ball (8.3%) and thermal balloon ablation (8.9%). Rates of dissatisfaction were high in both the roller ball ablation (33%) and thermal ablation (39%) groups.[95]

Potential Harms of Endometrial Ablation

The endometrial ablation procedure using roller ball necessitates general anesthesia whereas the thermal balloon ablation procedure can be conducted under local anesthesia. The rate of intraoperative complications was correspondingly higher in the group who underwent the more invasive procedure (5 including one case of cervical injury). There were no intraprocedural complications reported in the thermal ablation group. However, overall rates of patient satisfaction were equally poor as noted above.[95]

Endometrial Ablation Summary

Evidence is insuffcient to assess the effectiveness of abalation in improving fibroid symptoms.

Myomectomy

We included 19 studies that assessed myomectomy for treatment of uterine fibroids.[29,34,39,40,44-46,50,54,55,59,64,66,72,74,77,93,97,104] Of these, 13 studies reported final health outcomes following myomectomy for fibroids and met our inclusion criteria.[34,39,44,46,50,54,66,72,74,77,93,97,104] Six studies reported harms only.[29,40,45,55,59,64] We considered four RCTs to be good quality and six to be fair

quality and nine to be poor quality for effectiveness outcomes. Myomectomy techniques include laparoscopic myomectomy, laparotomic myomectomy, mini-laparotomic myomectomy, and hysteroscopic myomectomy.

Effects of Myomectomy on Fibroid Characteristics

Because fibroids are removed at the time of myomectomy fibroid and uterine volume are reduced. Fibroid recurrence was reported in seven studies with duration of followup ranging from 6 to 40 months.[46,54,74,77,93,97,104] No recurrences were reported in two studies that evaluated 114 women by ultrasonography 6 months following myomectomy.[54,74] In five studies, recurrence rates ranged from 2.5 to 24.7 percent (56 recurrences reported in 456 women). Recurrence rates did not differ by type of incision in four studies that compared different surgical procedures.[74,77,93,97,104]

Effects of Myomectomy on Bleeding

A single study with two-year followup data reported persistent abnormal menstruation in three (1.9%) women.[46] No other studies reported changes in symptomatic fibroid-related bleeding, such as heaviness of menses or total days of bleeding. Lack of this outcome means evidence is insufficient for determining if myomectomy improves an extremely common concern among women who seek intervention for fibroids.

Effects of Myomectomy on Fibroid-Related Pain

No studies of myomectomy reported fibroid-related pain outcomes.

Other Treatment Effects of Myomectomy

Return to usual activity

Recovery time ranged from 15 days up an average of 30 days as reported in three studies.[74,77,104] Type of incision was a major determinant in recovery time in two studies with more women reporting feeling fully recovered by day 15 following laparoscopy compared to minilaparotomy[74] or abdominal myomectomy.[104] Recovery time from myomectomy averaged 30 days in another small study.[77]

Quality of life and symptom status

Improvement in quality of life or symptom status was reported in four studies.[44,46,50,124] Quality of life significantly improved in both studies that assessed it. The FUME trial comparing myomectomy to UAE reported improved quality of life for both groups after one year as measured by the UFS-QOL.[44] A large Chinese study reported improvements in all four domains (physical, psychological, environment, and social relationship) after two years following laparoscopic uterine artery occlusion plus myomectomy using the WHOQOL-BREF measure. Measures of symptom status reported in two studies were not well described. Symptom relief from six symptoms including menorrhagia, dysmenorrhea, dyspareunia, pelvic pain, dysuria, and pressure improved for 88 percent (51/58) women after six months assessed by a questionnaire.[124] Symptom improvement including constipation, urinary frequency and menorrhagia improved for 85 percent of women postoperatively in a study evaluating loop ligation for women with larger fibroids.[50]

Effects of Myomectomy on Pregnancy Outcomes

Fertility and pregnancy

One study described no significant difference in pregnancy outcomes following laparoscopic myomectomy (54%) compared with laparotomic myomectomy (56%).[97] An RCT (n=136) compared laparoscopic myomectomy with mini-laparotomic myomectomy and assessed 12-month reproductive outcomes for a total of 556 and 669 cycles, respectively.[66] There was no significant difference in the cumulative pregnancy rate, or the cumulative live-birth rate. However, the time to first pregnancy (5 months vs. 6 months) and live birth (14 months vs.15 months) was significantly lower after laparoscopic myomectomy compared with mini-laparotomic myomectomy. A post-hoc subgroup analysis reported that in patients with symptomatic fibroids, the cumulative pregnancy rate, pregnancy rate per cycle (11.1% vs. 5.4%) and live-birth rate per cycle (9.9% vs. 4.8%) were significantly higher following laparoscopic myomectomy, compared with mini-laparotomic myomectomy. In patients with symptomatic fibroids, the times to first pregnancy and live birth were significantly lower after laparoscopic myomectomy, compared with mini-laparotomic myomectomy. In patients with unexplained infertility, no difference in any reproductive outcomes assessed was observed between the laparoscopic myomectomy and the mini-laparotomic myomectomy groups.[66]

An RCT with 181 women with fibroids who had been trying to conceive for at least 1 year without success, subdivided the women according to the location of the fibroid, (submucous, intramural, subserosal), and randomized to myomectomy (laparoscopic myomectomy or HSM) or no surgery.[72] For women with subserosal or intramural fibroids, there was no significant difference in the pregnancy rate, comparing myomectomy with no treatment. For women with submucous fibroids, the group who underwent myomectomy had a greater pregnancy rate (40.4%) than those who did not undergo surgery (21.4%).[72] Of a subset of women who attempted to conceive following myomectomy, 31 of 40 were pregnant at 13 months after fibroid removal and the delivery rate was 47.5 percent (19/40).[124]

Potential Harms of Myomectomy

Transfusion

Following treatment for fibroids with myomectomy, transfusion rates were most often zero (1040 participants in 15 arms from 11 studies).[34,40,45,50,54,64,74,93,97] Five studies[39,45,50,77,97] reported 18 transfusions among 410 participants treated by myomectomy (see Appendix H for details). Four studies did not report transfusion following myomectomy.[29,44,55,59] One study reported no significant difference in transfusion outcomes following laparoscopic myomectomy compared with laparotomic myomectomy.[97] One study reported no significant difference in transfusion outcomes following laparoscopic myomectomy plus uterine artery occlusion compared with laparoscopic myomectomy.[40] One study reported fewer transfusions following gasless laparoscopic myomectomy compared with conventional laparoscopic myomectomy.[45]

Perforation of organs

One study reported no significant difference in organ perforation (zero) following isobaric laparoscopic assisted laparotomic myomectomy compared with mini-laparotomic myomectomy but was likely underpowered to detect comparability.[55] One study (n=148) reported injuries to

pelvic organs, with no significant difference between laparoscopic myomectomy and mini-laparotomic myomectomy.[74]

Readmission

One study reported no significant difference in readmission or reoperation (zero) following isobaric laparoscopic assisted laparotomic myomectomy compared with mini-laparotomic myomectomy.[55] One study reported that one woman had acute peritonitis and underwent abdominal surgery 10 days after laparoscopic myomectomy, with no complications following mini-laparotomic myomectomy.[74] The Mara trial[124] reported just one readmission (1.6%) within 30 days after myomectomy.

Reintervention

One study reported higher reintervention rate after mini-laparotomic myomectomy (9%) compared with laparoscopic myomectomy (0%).[66] The reintervention rate was 3.2 and 4.0 percent due to fibroid recurrence in one study[124] and need for subsequent hysterectomy 7 months after myomectomy in a second study.[44]

Total complications

One study reported higher total complication rate after mini-laparotomic myomectomy (16%) compared with laparoscopic myomectomy (3%).[66] The FUME trial [44] reported six major complications (8%) all occurring during the hospital stay after myomectomy while another trial reported unexpected intra-uterine penetration after myomectomy in three cases.[124]

Myomectomy Summary

There is moderate strength of evidence that women reported improved quality of life following myomectomy. This procedure is an option for women desiring future fertility. There is some risk of fibroid recurrence (reported ranges from 0- 25%) that does not vary by type of surgical technique. Women undergoing laparoscopic procedures reported a faster return to usual activities.

Hysterectomy

We identified 14 studies[28,46,52,58,75,78,82-84,88,89,94,98,100] assessing hysterectomy in women with uterine fibroids. Seven reported harms only (i.e., did not report final health outcomes for effectiveness).[28,58,83,88,89,94,98] One study[100] did not report results reported for the women who were randomized to immediate hysterectomy; the results from the comparator arm, women treated with a GnRH to prevent or delay need for hysterectomy, is reported in the medication section above and in the comparative effectiveness section below.

Studies addressed the following interventions: intrafascial supracervical hysterectomy,[46] laparoscopic assisted vaginal hysterectomy,[28,58,83,89,94,98] total laparoscopic hysterectomy,[28,88] vaginal hysterectomy,[28,58,75,83,84,94,98] and total abdominal hysterectomy.[75,82-84,88] Three studies used more than one hysterectomy approach (e.g., type and route not standardized) or did not describe the type of hysterectomy.[52,78,100] Assessment duration (where clearly reported) in comparative studies ranged from 15 days to 24 months. We assessed five as good quality,[28,58,78,83,84] three as fair quality,[82,94,98] and six as poor quality for effectiveness outcomes.[46,52,75,88,89,100]

Effects of Hysterectomy on Bleeding

Two studies reported increases in hemoglobin levels at 24 months after surgery (Table 27).[52,78,127]

Table 27. Hysterectomy changes in hemoglobin [a]

Author, Year	Arm Description	N	Followup	Baseline; Followup (g/dl)	Change (g/dl)
Ruuskanen A et al. (2010)[52]	Hysterectomy	30	24 months	122.9 ± 21.7[b] NR	↑20.0 ± 20.7[b] p=NR
Hehenkamp WJ et al. (2005);[78] Volkers et al. (2007)[127]	Hysterectomy	73	24 months	NR NR	↑2.03 p<0.0001

Notes: [a] estimated intraoperative blood loss; [b] reported as g/L; Hemoglobin not reported in 11 studies: Ferrari MM et al. (2000);[98] Hwang JL et al. (2002);[83] Liu M et al. (2011);[46] Parazzini F et al. (1999);[100] Pinto I et al. (2003);[82] Seracchioli R et al. (2002);[88] Sesti F et al. (2008);[58] Sesti F et al. (2014);[28] Silva-Filho AL et al. (2006);[75] Soriano D et al. (2001);[94] Yen YK et al. (2002).[89] Benassi L et al. (2002)[84] reported hemoglobin change postoperative only. **Abbreviations:** n=number; NR=Not reported; g/dL= grams per deciliter

Effects of Hysterectomy on Fibroid-Related Pain

At 24 months after hysterectomy, 7 percent of women reported dysmenorrhea and 10 percent reported lower abdominal pain (intention to treat analysis with last valid observation carried forward).[52] A majority (78%) of the women who had lower abdominal pain at baseline reported improvement at 24 months after hysterectomy.[127] Of those without pain at baseline (n=14), one woman reported worsening of symptoms after hysterectomy.[127]

Other Treatment Effects of Hysterectomy

Return to usual activity

Mean time to return to work or usual activity ranged from 22 to 41 days as reported in four studies.[52,82,83,88] Women who received a vaginal or laparoscopic vaginal hysterectomy had a significantly faster recovery (mean 22 to 30 days) compared to total abdominal hysterectomy (mean 36 to 41 days) as reported in two studies[83,88] Mean recovery time for abdominal hysterectomy averaged 37 days in another study [82] and 35 days in another study that used a variety of surgical procedures.[52]

Quality of life and symptom status

Improvements in quality of life or symptom status were reported in four trials. Two studies reported short terms results (1-month post surgery) [75,84] and two studies reported results after 24 months.[46,123,] The short term results were available from two studies that compared vaginal to abdominal hysterectomy in 179 women. Quality of life assessed by the SF-36 form was better for women receiving vaginal hysterectomy compared to abdominal hysterectomy[75] and patient satisfaction with treatment assessed using an unvalidated questionnaire was higher for women following vaginal surgery.[84] Quality of life was significantly improved after two years as reported in the EMMY trial[123] assessed by HRQOL and SF-36 and a Chinese study reported improvements in health-related quality of life as measured by the WHOQOL-BREF questionnaire.[46]

Potential Harms of Hysterectomy

Transfusion

The rate of transfusion following hysterectomy ranged from zero to 20 percent in 890 women from 11 studies (Table 28). Six studies reported no significant difference in transfusion outcomes following different hysterectomy interventions for fibroids: laparoscopic assisted vaginal hysterectomy versus total abdominal hysterectomy,[98] vaginal hysterectomy versus total abdominal hysterectomy,[75] vaginal hysterectomy versus laparoscopic assisted vaginal hysterectomy,[28,94] total laparoscopic hysterectomy versus total abdominal hysterectomy,[88] total laparoscopic hysterectomy versus laparoscopic assisted vaginal hysterectomy,[28] and vaginal hysterectomy versus total laparoscopic hysterectomy.[28] Authors reported 5 percent (3/61) of patients randomized to laparoscopic hysterectomy with bipolar coagulation of uterine vessels or laparoscopic hysterectomy alone required transfusion.[89]

Table 28. Studies (n=11) reporting transfusion following hysterectomy

Author, Year	Hysterectomy	Women transfused	Total N	Risk (%)
Benassi L et al. (2002)[84]	hysterectomy, abdominal	4	59	6.8
Benassi L et al. (2002)[84]	hysterectomy, vaginal	2	60	3.3
Ferrari MM et al. (2000)[98]	hysterectomy, laparoscopic assisted vaginal	0	31	0
Ferrari MM et al. (2000)[98]	hysterectomy, vaginal	1	31	3
Hehenkamp WJ et al. (2005)[78]	Hysterectomy	10	89	13.3
Hwang JL et al. (2002)[83]	hysterectomy, abdominal	1	30	3.3
Hwang JL et al. (2002)[83]	hysterectomy, laparoscopic assisted vaginal	5	30	16.7
Hwang JL et al. (2002)[83]	hysterectomy, vaginal	1	30	3.3
Pinto I et al. (2003)[82]	hysterectomy, abdominal	4	20	20.0
Seracchioli R et al. (2002)[88]	hysterectomy, abdominal	1	62	1.6
Seracchioli R et al. (2002)[88]	hysterectomy, total laparoscopic	0	60	0
Sesti F et al. (2008)[58]	hysterectomy, laparoscopic assisted vaginal	0	40	0
Sesti F et al. (2008)[58]	hysterectomy, vaginal	0	40	0
Sesti F et al. (2014)[28]	hysterectomy, laparoscopic assisted vaginal	2	36	5.6
Sesti F et al. (2014)[28]	hysterectomy, total laparoscopic	0	36	0
Sesti F et al. (2014)[28]	hysterectomy, vaginal	0	36	0
Silva-Filho AL et al. (2006)[75]	hysterectomy, total abdominal + hysterectomy, vaginal*	1	60	1.7
Soriano D et al. (2001)[94]	hysterectomy, laparoscopic assisted vaginal	1	40	2.7
Soriano D et al. (2001)[94]	hysterectomy, vaginal	1	40	2.5
Yen YK et al. (2002)[89]	hysterectomy, laparoscopic assisted vaginal	2	32	6.3
Yen YK et al. (2002)[89]	hysterectomy, laparoscopic assisted vaginal with bipolar coagulation of uterine vessels	1	29	3.4

N is the number analyzed. The number analyzed was equal to the number randomized in all arms. *One study reported transfusion counts for both groups. Transfusion counts include both intraoperative and postoperative.

Thromboembolism

Two thromboembolic events (1 pulmonary embolism and 1 deep vein thrombosis) were reported following hysterectomy in 227 patients from four studies that reported thromboembolism.[78,82,84]

Perforation of organs

Two studies reported no organ perforation following different hysterectomy interventions for fibroids.[75,84] One RCT reported that one woman randomized to total laparoscopic hysterectomy was converted to total abdominal hysterectomy because of intraoperative bowel injury.[88]

Hysterectomy Summary

Overall, patient satisfaction and recovery time following hysterectomy was better for women who received a vaginal hysterectomy compared to total abdominal hysterectomy. Harms, including the need for blood transfusion and organ perforation were similar for all types of hysterectomy.

Hysterectomy or Myomectomy

We found three studies, one fair quality[69] and two poor quality,[42,110] that randomized women to either myomectomy or hysterectomy. Two studies compared UAE to myomectomy or hysterectomy[42,69] and one study compared a GnRH agonist to myomectomy or hysterectomy.[110] Quality of life was the primary outcome for both studies comparing UAE to surgery. In the REST trial scores on the SF-36 and the EQ-5D™ were significantly improved after 12 months.[69] In the Jun trial there was limited improvement for the surgery group after 6 months as assessed by the SF-36 questionnaire. Scores were improved for the mental health and vitality measures only, while physical health, social function and emotional role were almost unchanged.[42] Symptom improvement and fertility outcomes were reported in the study comparing buserelin to immediate surgery.[110] Three of five women who underwent myomectomy for infertility had term pregnancies.

Surgical Intervention Summary

Most of these studies did not follow patients beyond the postoperative period. Therefore, many studies did not report patient-specific, or symptom related outcomes such as change in fibroid related pain or fibroid-related bleeding. Many of the studies with surgical or procedural interventions reported intermediate outcomes such as technical success, hospital length of stay, or estimates of blood loss related to the invasive procedure (e.g., postoperative hemoglobin, intra or postoperative transfusion rate). While these are important features they do not provide evidence that women want about the likely outcomes of surgery for fibroids such as relief from symptoms, improvement in quality of life, and sexual function.

Comparative Effectiveness Studies

Content of Literature for Comparing Effectiveness of Interventions

Direct comparisons of alternative treatment strategies are crucial to support informed decisions among medical care options. Women and their care providers need unbiased comparisons across similar groups of women achieved by random assignment to different interventions that assess the same outcomes with the same yardstick. In total 18 studies compared the effectiveness of different categories of interventions.[29,39,42,44,46,51-53,67,69,77,78,82,87,90,99,100,114] Available comparisons are summarized in Table 29. When different approaches to the same general type of intervention were compared within a category, for instance uterine artery ligation compared to uterine artery embolization, or laparoscopic myomectomy compared to myomectomy via mini-laparotomy, those findings are reviewed in the

sections above that summarize outcomes within the category of intervention type. Here we review comparisons across types of interventions.

Table 29. Randomized trial comparisons across categories of interventions

Method	Medical	Ultrasound Ablation	Vascular Occlusion	Radiofrequency Ablation	Myomectomy	Hysterectomy	Count
Medical	5[53,67,87,99,114]	0	0		0	1[100]	**6**
Ultrasound Ablation			0	1[51]	1[39]	0	**2**
Vascular Occlusion			1^[90]		2[44,77]	5[42,52,69,78,82]	**8**
Radiofrequency Ablation					1[29]	0	**1**
Myomectomy						1[46]	**1**
Hysterectomy							**0**
Count	**5**	**0**	**1**	**1**	**4**	**7**	**18**

^#5186 reviewed with surgical comparisons as vascular occlusion was done via laparoscope.

Comparisons of Medical Management

We identified five studies designed to compare outcomes across different categories of drugs.[53,67,87,99,114] Two studies compared a GnRH agonist to a hormone replacement regimen for use among postmenopausal women with fibroids.[87,99] Two compared a GnRH agonist to cabergoline which is a dopamine receptor agonist.[53,67] The fifth compared progesterone delivered locally to the endometrium by a levonorgestrel intrauterine device to daily oral progesterone.[114] These studies were small and inadequately powered for providing definitive evidence; they are briefly described below. A single study randomized women interested in hysterectomy to immediate hysterectomy or goserelin to determine if medical management allowed some women to avoid surgery.[100]

Comparison of GnRH agonist to cabergoline

The GnRH agonist used in these studies (Diphereline) is not available in the United States, however similar drugs are. Cabergoline, which is indicated for treatment of prolactinomas, is available in the United States for off-label use and has been shown in animal and tissue models as well as case series in women to diminish growth of uterine fibroids. In both trials, conducted in Iran by the same research team with a similar protocol, women in the GnRH groups received a month of treatment and those receiving cabergoline, six weeks of treatment.[53,67] Fibroid volume decreased in both groups and was not statistically different.[53,67] Those on GnRH agonists were more likely to stop having menses and to have hot flashes (typical side effects of the drug). Women in both arms experienced a decrease in days of bleeding compared to baseline, with the least days among those using the GnRH agonist.[53,67] Pain was similarly reduced in both groups.[53,67] Side effects of GnRH matched those review above; cabergoline was associated with headaches and nausea in the first week of use.[53,67] In summary the GnRH agonist and cabergoline delivered similar results for reducing fibroid size and pain. Since GnRH agonist create a medical menopause, menopause-like side effects were more common in that arm than

cabergoline, while the latter had an initial period of nausea, vomiting, and dizziness, which caused one woman to discontinue treatment, compared to none in the GnRH group.[53,67]

Comparison of GnRH agonist to hormone replacement regimens

These two trials by a Turkish team and an Italian team, compared tibolone (a GnRH agonist not available in the United States) to transdermal hormone replacement systems with a similar dose of estrogen and 12 versus 14 days of progestin supplementation.[87,99] The rationale for the studies was to determine if the GnRH agonist would prove a viable alternative to conventional HRT that did not promote growth of fibroids in postmenopausal women. Neither provided power calculations and study size was 38 and 46 participants randomized equally. Thus, power to detect differences in the primary outcome of uterine size was limited. At 6 months, mean fibroid volume was not different between baseline (23.1 ± 3.6 cm^3) and completion of treatment (27.2 ± 3.9 cm^3) for the HRT group or for the tibolone group (18.6 ± 4.1 cm^3 vs. 20.1 ± 4.0 cm^3).[87] The trial that examined 12 months of treatment reported a statistically significant within group change in size of the largest fibroid, from 26.8 ± 12.5 to 35.8 ± 0.17 cm^3, in the HRT group and no change in the GnRH agonist group. The comparison across groups was not significant and the change noted is not likely to be clinically significant.[99] These findings are compatible with a prior review that included cohort studies and found moderate evidence that HRT does not increase size of fibroids.[17]

Comparisons of oral versus IUD delivered progesterone

This Turkish study randomly assigned 30 women each to daily norethindrone acetate (NETA) or levonorgestrel IUD with a goal of determining which strategy was superior for improving bleeding patterns among premenopausal women with fibroids who had declined surgery.[114] Participants used a standardized pictorial method for reporting blood loss in a diary over the course of treatment. No placebo was used and women were not blind to intervention group. Visual blood loss scores improved by six months in both groups, with greater improvement in the IUD group which was reported to be statistically significant. Improvement in hemoglobin likewise occurred in both groups with a statistically greater improvement among those with an IUD. Women with the IUD were more satisfied and more likely to continue treatment. Risks of these treatments have been better reviewed in the separate literatures about each type. This trial suggests local control of bleeding with an IUD can be successful even among women whose fibroid symptoms were considered appropriate for surgical intervention. However, the quality of the study was poor and thus evidence to guide care is insufficient.

Comparison of goserelin to immediate hysterectomy

Seventy-two premenopausal women older than 45, with at least one fibroid larger than 10 cm diameter, heavy menses for three months or longer, and who were eligible for hysterectomy were randomized to immediate surgery (n=13) or treatment with goserelin, a GnRH agonist (n=59).[100] The treatment was given in the form of a depo injection of 3.6 mg each month for three months. Participants were followed for three years and allowed up to two-more rounds of treatment if their bone mineral density was not at risk. Those on medication could opt for hysterectomy at any time. Of the 59 women assigned to medication, five chose hysterectomy within three months and by one year a little over 20 percent of the total selected hysterectomy. By the end of the third year 39 percent had continued to hysterectomy (95% CI: 26 to 62), suggesting as much as 60 percent of similar women might avoid hysterectomy for three years of more. The quality of this

study was judged to be poor in part because of lack of masking of researchers and participants to assigned intervention; however, if participants were inclined to want surgery this bias would tend to increase the proportion who opted for hysterectomy rather than forestall that choice. The evidence is intriguing but insufficient to encourage selection of medication if hysterectomy is planned.

Comparisons of Procedures

The least invasive procedure for fibroids is ultrasound ablation. No instruments pass through the skin. A single system (Exablate) produced by InSightec (privately held by General Electric Healthcare) and termed MRI guided focused ultrasound is approved in the United States for focused ultrasound ablation of fibroids. This system was not used in any direct comparison studies. Two studies compared high intensity focused ultrasound guided by real time ultrasound, sometimes termed HIFU, to alternate interventions: one to use of an electrode inserted through the skin into the fibroid,[51] and another to myomectomy which is a surgical procedure.[39] Both are reviewed here rather than with surgeries.

Other direct comparisons of procedures included two comparisons of UAE to myomectomy,[44,77] three comparisons of UAE to hysterectomy,[52,78,82] and two comparisons to participants who had either myomectomy or hysterectomy.[42,69]

Comparisons of high intensity ultrasound to radiofrequency ablation

An ultrasound treatment unit designed to treat tumors was used for this RCT. The system combines ability to visualize fibroids while at the same time targeting them with high frequency ultrasound (HIFU) waves to ablate the fibroid. Among premenopausal women, they compared HIFU to radiofrequency ablation by insertion of a specialized electrode into the fibroid through the skin. The electrode was guided by ultrasound and positioned in the fibroid. The electrode uses radiofrequency to destroy tissue via heating it. Both techniques were evaluated during the procedure for ability to destroy the fibroid tissue. Of fifty women per group, 58 percent of those treated with HIFU had complete ablation of the tumor, compared to 90 percent with radiofrequency ablation. This outcome was documented at the end of the procedure ($p<0.05$).[51] For both procedures larger fibroids were less likely to be fully ablated. No serious complications occurred in either group. Followup of fibroids and symptom resolution were not studied so evidence is insufficient to guide choice among these options.

Comparisons of high intensity ultrasound to myomectomy

This RCT also used a HIFU system developed for cancer treatment.[39] The HIFU therapy was visualized in real-time using ultrasound and completeness was assessed by grey-scale visualization of the degree of destruction of the fibroid target(s). Conventional myomectomies were performed by the same group of surgeons. Fifty-five women were randomized to each arm; only results for women who completed followup (n=48 HIFU and n=52 myomectomy) are reported. The primary outcome for this trial was sexual function, which was comparable in both groups at conclusion of 6 months of followup and consistent with return to pre-intervention baseline. The primary differences across groups reflect the difference in invasiveness of the procedures and are related to the risks of surgery. Women having HIFU had shorter hospitalizations, earlier ambulation, and faster recovery; they had no blood loss and no surgery-related symptoms.[39,115] Fibroid outcomes and symptom resolution were not studied so evidence is insufficient to help chose between options.

Comparisons of UAE to myomectomy

Two European RCTs reported in three publications[44,77,124] compared UAE to myomectomy. The studies included 284 women ages 31 to 50 years with fibroids measuring 4 to 12 cm in diameter; 96 percent of participants had symptoms, some had only fertility concerns. In total there were 121 embolizations and 122 myomectomies with followup. Technical success was similar.[124] Embolization is a minimally invasive vascular radiology procedure, thus length of stay is significantly shorter for UAE averaging around two days compared to four to six days, and blood loss was associated only with myomectomy surgeries.[44,124] Time away from work was at least 10 days shorter for those who had UAE compared to myomectomy.[124]

By 6 months, women in the UAE group had more subsequent interventions (re-embolizations and myomectomies) compared to repeat procedures in the myomectomy group (32.8% vs. 3.2%, $p<0.0001$). Symptom relief (88.5% vs. 87.9%) was similar between groups. For myomectomy, fibroids were removed so change in size is not relevant. Among those with UAE, significant reduction of fibroid volume (58.7%) and size (31.7%) was achieved.

One year after treatment, both UAE and myomectomy groups had significant improvements in quality of life compared to their baseline (measured by the UFS-QOL) without difference in the degree of improvement across groups ($p=0.14$).[44] Rates of subsequent intervention continued to be higher after UAE (14.8%) than after myomectomy (4%), $p<0.0001$; while risk of fibroid recurrence was not statistically different suggesting differences in recurrence do not drive the higher likelihood of additional intervention among those with UAE. Since satisfaction and quality of life are similar and recurrence is similar, this indicates the cause of additional interventions among those with UAE is yet to be clearly defined.

Reproductive outcomes were reported for 66 women (26 after UAE and 40 after myomectomy) in one study.[77,124] After two years the pregnancy rates were significantly higher after myomectomy (78% vs. 50%, $p<0.05$) while miscarriage rates were higher after UAE (64% vs. 23%, $p<0.05$). Nineteen percent of women who had UAE had live births compared to 48 percent after myomectomy ($p<0.05$).[124]

In summary, two small studies of fair quality, suggest UAE achieved similar results to myomectomy except for future reproductive outcomes which low strength of evidence suggests are worse for pregnancies conceived after UAE. Low strength of evidence also suggest women who have UAE may be more likely to have future interventions though this is not explained by risk of fibroid recurrence, differences in quality of life, or satisfaction with outcomes.

Comparisons of UAE to hysterectomy

Three RCTs comparing UAE with hysterectomy are published in 12 reports. Study participants were all from Europe. The EMMY trial[78,116,119,122,123,125-127,129,130] is a multicenter trial (28 hospitals) conducted in the Netherlands. A Spanish trial by Pinto and colleagues[82] and a trial from Finland by Ruuskanen and colleagues[52] were single-center trials. Combined these studies included 291 women ages 33 to 57 years with symptomatic uterine fibroids, who were candidates for hysterectomy. The EMMY trial excluded women with submucosal leiomyoma while the Spanish trial excluded women with leiomyomas larger than 10 cm in diameter. The third trial[52] did not exclude women based on the size or location of fibroids. Across studies, 153 women were allocated to UAE and 138 to hysterectomy. Followup duration of these three trials varied from 6 months[82] to 2 years[52,147] and 5 years.[119]

Early procedure outcomes and recovery

Blood loss from the procedure was negligible for UAE and higher for hysterectomy.[78] In the surgical group of the Finnish trial,[52] 19 percent of the vaginal or laparoscopic hysterectomies were converted to abdominal hysterectomy due to technical difficulties; and the EMMY trial reported four conversions of laparoscopic or vaginal hysterectomy to laparotomy (5.3%).[78] Length of hospital stay was shorter ($p<0.001$) for UAE (1.3 to 1.7 days) compared with hysterectomy (3.5 to 5.9 days).[52,78,82] Re-admission rates were the same (5%) in both arms of the Spanish study[82] while the EMMY trial reported significantly higher near term re-admission rates after UAE (11% vs. 0%, $p<0.003$) compared to hysterectomy.[78,129] Despite this, time to return to usual activities was significantly ($p<0.001$) shorter in the UAE group (fewer than 20 days) compared to hysterectomy group (more than 30 days).[52,78,82]

Fibroid characteristics

In the UAE groups, effects on fibroid characteristics were similar to the overall literature about the effectiveness of UAE. At six months fibroid volume was 44 to 46 percent decreased,[82,127] and at two years, the EMMY trial reported total uterine volume was reduced 48.2 percent (95% CI: 39.2 to 57.1) and dominant fibroid volume 60.5 percent (95% CI: 46.1 to 75.0).[127] The Finnish study did not repeat imaging to document final fibroid characteristics at two years.[52]

Bleeding

Likewise, improvement in bleeding was similar to the overall literature about effectiveness of UAE. The Spanish trial reported heavy and/or irregular bleeding resolved in 86 percent of women, three women (8%) reported no improvement in bleeding while 6 percent reported worsening of bleeding after 6 months of followup[82] Among those who presented with menorrhagia in the Finish RCT, 67 percent had total or substantial improvement in the UAE group versus 100 percent after hysterectomy ($p=0.002$).[52] Among EMMY participants, 71.6 percent were symptom free at five years with respect to problem bleeding, while 11 percent reported great or moderate improvement, and 10 percent responded that their symptoms were unchanged.[119]

By definition, women who have hysterectomy achieve amenorrhea, which is absence of menses. Across studies among women who had UAE, 14 to 17 percent reported amenorrhea at 6 months follow-up.[82,127] At 2 years of followup 37 percent of EMMY UAE patients had no menses and this increased to 40.7 by 5 years, however in total 28 percent of amenorrhea was attributable to hysterectomies and 12 percent to reaching menopause.[119,127] Increase in hemoglobin levels from baseline at two years was significantly higher for hysterectomy group compared to UAE group (increasing 2.03 vs. 1.37 g/dL, $p=0.037$) in EMMY[127] but not in the Finnish trial ($p=0.16$)[52] which may reflect inadequate power to detect modest differences.

Symptoms

Overall relief of symptoms was good across groups (82% UAE vs. 93% hysterectomy, $p=0.173$) in the Finnish study at 2 years.[52] Greater improvement in pressure symptoms was reported after UAE (95%) compared to 69 percent in the hysterectomy group ($p=0.03$);[52] and more urinary bladder symptoms were reported after hysterectomy than after UAE (30% vs. 7%, $p=0.03$). Regarding pain, there was a significant decrease from baseline at all time points ($p\leq0.03$) and by 24 months women reported similar improvement of pain (84.9% after UAE vs.

78% after hysterectomy, p=0.30).[127] The EMMY trial captured symptoms predominantly in a panel of quality of life measures.

Quality of life

Overall health related quality of life improved in both trial arms and was comparable across groups in EMMY by completion of five years of followup.[119] One secondary outcome (change in bowel movements) was worse in the hysterectomy group than UAE at 5 years from baseline (p=0.01) while the UAE group had improvement from 6 month onwards.[119] Body image scores improved significantly more in UAE group earlier than in hysterectomy group who did not show any change at 6 months, (p=0.02) but there was no group difference in body image or sexual function scores at 24 months or later.[119]

Subsequent treatment

Subsequent treatment rates were higher in the UAE group than in the hysterectomy group at each time point in followup (Table 30).[44,52,78] The EMMY trial reported significantly higher rates of any subsequent gynecologic intervention (9.8 percent, 17.3 percent, 28.3 percent, and 34.6 percent) after UAE versus 1.3 percent, 5.3 percent, 8.0 percent, and 10.7 percent after hysterectomy at 6-month, 1-year, 2-year, and 5-year followup, respectively.[119] Similar risk of additional intervention was reported at 2-year followup in another study (19.2% with UAE and 10.3% after hysterectomy, p=0.24).[52] A proportion of early reinterventions are repeat UAE, myomectomy, or hysterectomy among the small percentage of women (1.0% to 4.9%) for whom effective occlusion of the uterine vessels could not be achieved at the time of the initial procedure.[44,78] These data are included in the meta-analysis of subsequent intervention.

Table 30. Satisfaction in studies of UAE versus hysterectomy

Measure	Author, Year	Time (months)	UAE (%)	Hysterectomy (%)	P value
Very satisfied	Hehenkamp WJ et al. (2008)[123]	1.5	28.4	44.0	NS*
		6	35.8	56.0	NS*
		12	35.8	64.0	p=0.001*
		18	40.7	57.3	p=0.184*
		24	42.0	60.0	p=0.02*
	van der Kooij SM et al. (2010)[119]	60	45.7	66.0	p=0.13*
Satisfied	Hehenkamp WJ et al. (2008)[123]	1.5	NR	NR	NR*
		6	NR	NR	NR*
	Pinto I et al. (2003)[82]	6	77.7	88.2	NR
	Hehenkamp WJ et al. (2008)[123]	12	64.1	88.6	NR
		18	NR	NR	NR*
		24	78.8	83.6	NR*
	Ruuskanen A et al. (2010)[52]	24	88.9	96.7	p=0.34
	van der Kooij SM et al. (2010)[119]	60	85.3	88.6	p=0.37

*p values reported for comparison across seven possible levels of satisfaction that include very satisfied and satisfied.
Abbreviations: NR=Not reported; NS=Not significant; UAE=uterine artery embolization

The proportion of women who received hysterectomy reported higher satisfaction rates after one (p=0.001) and two years (p=0.02) compared to women who received embolization but satisfaction levels for both groups were comparable by 5 years (p=0.13). Forty six percent of

women after UAE and 56 percent of women after hysterectomy were very satisfied with the outcome by 5 years (overall satisfaction: 84% vs. 88%, p=0.37).

Reproductive status

Ovarian reserve, pregnancy, and sexual function related outcomes were reported only in the EMMY trial.[126] Reduction in ovarian reserve was based on FSH and AMH hormone levels. Levels of FSH, suggested diminished reserves, increased from baseline (p=0.001) in both groups at 24 months follow-up but there was no group difference (p=0.32). The number of women with FSH greater than 40 IU/L, confirming menopause, at 24 months was 14/80 (18%) in the UAE group compared to 17 women (21%) in the hysterectomy group, with no differences over continued followup. The change scores of AMH levels from baseline were significantly different between the groups only at 6 weeks of treatment (p=0.005) and the AMH levels remained decreased only in the UAE group during the followup.

Harms

Harms are reviewed for each category of intervention within the sections for UAE and specific surgeries above.

Summary

Though subsequent intervention is more common after UAE than hysterectomy, the majority of women randomly assigned to have UAE avoided hysterectomy for the duration of followup, which included five years of surveillance in the largest study. Fewer than one in three women with UAE required additional treatment. For women who need to avoid longer hospitalization and recovery associated with hysterectomy or who wish to retain their uterus, moderate evidence supports UAE is a good alternative to resolve symptoms.

Comparisons of UAE to patient choice of myomectomy or hysterectomy

A larger, fair quality trial in the United Kingdom[69] and a poor quality study conducted in China[42] made this comparison. Combined, these studies randomly assigned 169 women to UAE and 115 women to conventional surgeries for uterine fibroids.[42,69] Both found UAE to have shorter hospital stay, shorter recovery time, and fewer serious complications (if subsequent treatment is not counted as a complication). In other words, UAE was associated with fewer complications at the time of the procedure but a greater proportion of women chose to have a different intervention in followup. Similar to the studies detailed above, the study that included one-year followup reported that among women assigned to UAE, 12.6 percent had subsequent interventions for inadequate control of symptoms. The Short Form Quality of Life 36 item measure was the primary outcome for this UK trial. At one month the UAE group has significant improvements in multiple areas of function, however by one year both groups had similar improvements, indicating the faster recovery for UAE is captured by the SF-36. In summary, these studies are in agreement with those that make comparison to hysterectomy only contributing to modest evidence that UAE has a shorter recovery and is as effective as surgery in major domains of patient outcomes. The primary caveat is that this comes with risk of subsequent intervention, which is also addressed in our meta-analysis.

Comparisons of Surgeries

The majority of surgical studies that made comparisons did so within a category of intervention, for instance comparing myomectomy conducted by laparoscopy to myomectomy

through a laparotomy incision. Both are intended to remove fibroids and the primary comparisons across approaches was typically made at the level of intermediate outcomes such as length of surgery, estimated blood loss, and length of hospital stay. These are reviewed within categories of interventions above and when clinically and statistically significant advantages have been demonstrated they are noted. Comparisons across types of surgical interventions were meager and the three related studies are noted below.

Comparison of laparoscopic bipolar coagulation with and without uterine nerve ablation

In this small (n=85), poor quality study of women with fibroids and pain with their menstrual periods, 41 women were randomly assigned to also have laparoscopic uterine nerve ablation at the time of laparoscopic occlusion of the uterine vessels.[90] Both groups had equal reduction in size of fibroids and in reduction of bulk symptoms from the vascular occlusion. Women in the nerve ablation group had less post-operative pain at one month as measured by a non-standardized 5-point scale ($p<0.05$) and by six months painful menses were improved in 92.1 percent of the nerve ablation group compared to 73.8 percent of the comparison group ($p<0.05$).[90] It is not clear whether subjects and interviewers were masked to treatment status for these analyses risking response bias. Thus, the results are intriguing but insufficient to inform a decision to include uterine nerve ablation at the time of coagulation of the uterine vessels.

Comparisons of laparoscopic thermal ablation to laparoscopic myomectomy

A small study compared laparoscopic use of a needle radiofrequency thermal ablation technique done through the laparoscope (n=26) to laparoscopic myomectomy (n=25).[29] Ultrasound was performed during the procedures to definitively identify fibroids and document immediate intervention outcome. Thermal ablation successfully treated 98.6 percent of fibroids while 80.3 percent of fibroids were able to be removed surgically. Blood loss was lower in the thermal ablation group. Time in hospital was shorter for the former, around 10 hours, compared to the myomectomy group who stayed around 30 hours ($p<0.001$) Fibroid outcomes and symptom resolution were not studied so evidence is insufficient to help chose between options.

Comparisons of myomectomy to hysterectomy

A single, moderate size study of poor quality, conducted in China compared laparoscopic uterine artery occlusion (n=158) with myomectomy to supracervical hysterectomy (n=174).[46] Supracervical hysterectomy removes the uterus but leaves the cervix in place.[46] This RCT was specifically designed to assess quality of life using the World Health Organization quality of life questionnaire which addresses four domains: physical, psychological, social relationships (including sexual function), and environment (home, finance, access to care, etc.) and an overall score. Higher scores indicate better quality of life. At two months after surgery, physical and social domains were superior in the myomectomy compared to the hysterectomy groups; no other areas were meaningfully different. By two years, myomectomy was superior to hysterectomy in all domains except environment ($p<0.01$) and both study groups had meaningful improvements compared to their baseline. Women treated with the myomectomy and uterine artery occlusion had a low (2.5%) fibroid recurrence rate by comparison with the literature however, no randomized comparison was available within this study.

In summary this single study provides insufficient strength of evidence that myomectomy with uterine artery occlusion is as good or better than supracervical hysterectomy for improving

quality of life in key functional domains related to physical, psychological, and relationship domains.

Comparison of Transfusion Rates

Transfusion rates were reported for 41 arms across 23 studies. Transfusion rates by intervention category are summarized in Table 31.

Table 31. Transfusion rates by intervention category

Intervention Category (Number of Arms)	Women Transfused	Total N	Rate (%)
Hysterectomy (18)	36	785	4.6
Hysterectomy or Myomectomy (1)	4	20	20.0
Myomectomy (18)	18	1286	1.4
Uterine artery embolization (3)	0	158	0.0
MRgFUS (1)	0	48	0.0
All (41)	58	2297	2.5

Analysis of Subsequent Treatment Following Initial Treatment for Uterine Fibroids

We estimated the probabilities of subsequently receiving additional treatment for fibroids after randomization to a given initial treatment of medication (Figure 5), embolization (Figure 6), or myomectomy (Figure 7) for uterine fibroids from data reported in 48 studies.[26,27,35,37,41-44,47,49,50,52-54,56,57,62,63,65,68-70,73,74,76-78,80,82,85-87,90-92,97,99,101-103,105,106,108-113] Subsequent treatments were grouped into these categories: 1) no intervention; 2) UAE; 3) IUD; 4) myomectomy 5) hysterectomy an 6) MRgFUS and 7) ablation (Appendix I). Rates of subsequent intervention ranged from zero up to 40 percent for women in their 30s, 40s, and 50s. Overall, fewer than half of women had another intervention within 24 months. Rates of subsequent intervention were lowest for initial medical management and higher following myomectomy or UAE. UAE was most often followed by myomectomy among those in their 30s. Younger women who initially had myomectomy were most likely to have repeat myomectomies over the two years of followup. After medical treatment, very few women in any age group had subsequent treatment within two years.

Figure 5. Estimates of probability of subsequent treatment following initial medical treatment for uterine fibroids

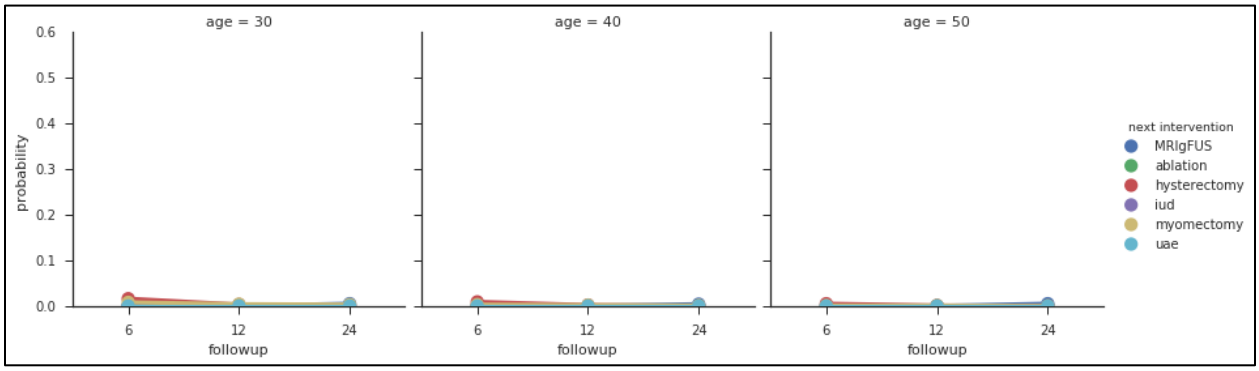


Figure 6. Estimates of probability of subsequent treatment following initial uterine artery embolization for uterine fibroids

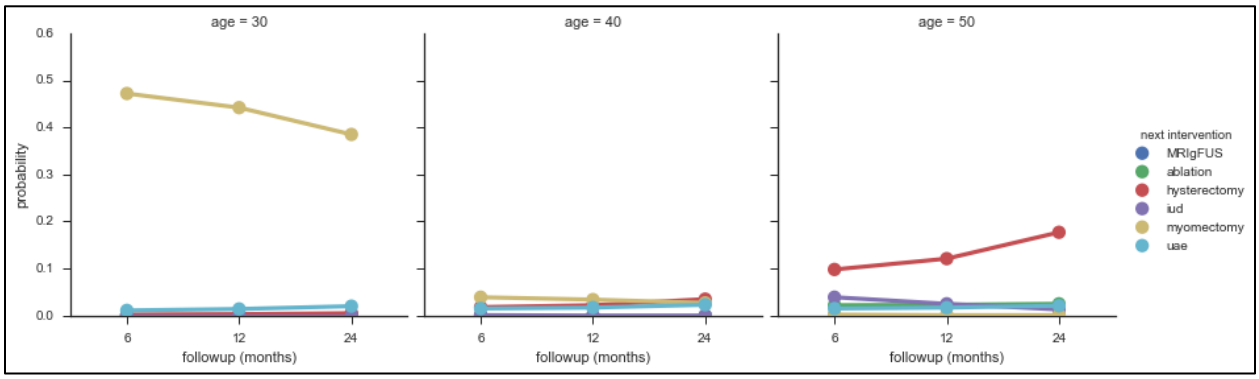
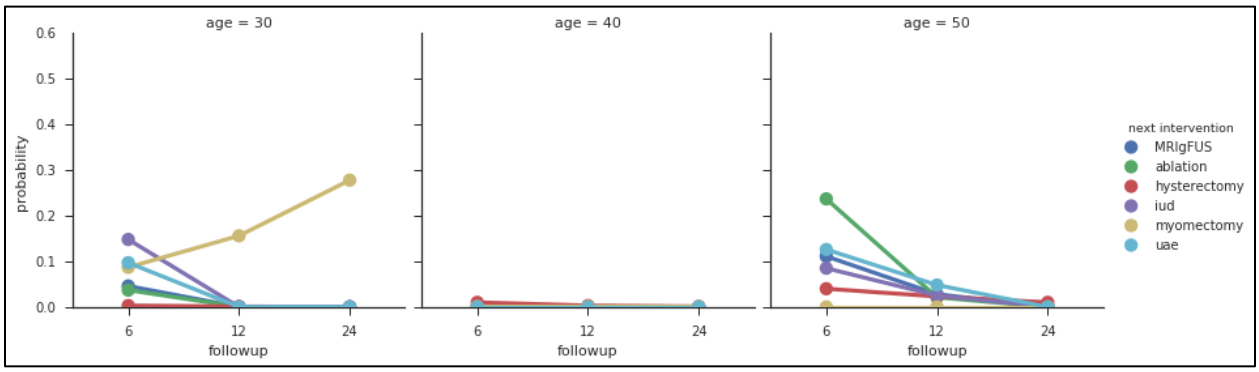


Figure 7. Estimates of probability of subsequent treatment following initial myomectomy treatment for uterine fibroids



Key Question 2. Treatment effect modifiers: patient and fibroid characteristics

KQ 2 Key Points

- Among 90 randomized clinical trials of interventions, none were explicitly designed to address whether intervention effectiveness varied by patient or fibroid characteristics.
- Six studies provided some information about influence of characteristics on outcomes within or across arms.
- None were statistically powered to examine effect modification by characteristics within arms to provide information that could be used to guide care based on individual or fibroid characteristics.

Description of Studies

For this KQ we systematically reviewed all included trials (n = 90) for each category of intervention. We sought: 1) indication that the study aimed to determine the influence of patient or fibroid characteristics on effectiveness and/or 2) described statistical analyses that allowed determination of whether patient of fibroid characteristics modified outcomes.

At its core, this question is about effect modification also called interaction. We sought to determine if specified subsets of participants within an arm are statistically determined to have a meaningful difference in outcomes. For instance if women with five or more fibroids are found to have less improvement of their hematocrit at six month after an intervention than those with fewer than five initial fibroids, and the p value for that comparison is significant, we would say there is effect modification of the effectiveness of the intervention by fibroid number such that women with fewer fibroids experience superior results for improvement in hematocrit. No studies were explicitly powered to investigate effect modification.

We identified only six trials that contributed related analyses: two pharmaceutical trials (in 3 publications),[81,86,131] two studies that compared UAE to surgery, each with multiple publications (REST[69,117,120] and EMMY[78,119,129]) , and one surgical trial.[72] One additional study addressed whether baseline characteristics influenced likelihood of success across procedure arms.[51] We assessed one study as good quality,[78,119,129] three as fair quality,[69,81,86,117,120,131] and two as poor quality.[51,72]

Detailed Synthesis

Pharmaceutical Intervention

In a dose comparisons trial of oral mifepristone (5 mg vs. 10 mg), the authors reported no difference in uterine fibroid volume size when analyses were adjusted for baseline volume, dose, and treatment duration (6 or 12 months). There was no significant difference in uterine volume reduction between the two dose groups (p=0.94). However in pooled analyses, for every 10 cc larger increment in baseline fibroid volume, fibroid volume reduction increased, on average, by 3.8 cc after adjusting for dose and time (95% CI: 2.7 to 4.9, p<0.001).[131]

Within a raloxifene arm (60 mg for 6 cycles) authors found the drug demonstrated selective action on leiomyoma by menopausal status, such that postmenopausal women were more likely to achieve decreased uterine and fibroid size. Thirteen of 31 postmenopausal women had decreased size of fibroids[91] compared to one of 29 premenopausal women.[86]

Procedural Interventions

Uterine Artery Embolization

In one of several followup studies from the REST trial comparing UAE to surgery (hysterectomy or myomectomy), the authors found that 5-year re-intervention rate after UAE did not differ (p=0.123) by the degree of infarction achieved during the initial procedure, as measured by MRI.[117] Study authors reported no effect of age (p=0.77), uterine volume (p=0.50) or fibroid diameter (p=0.57) on the degree of infarction as measured by MRI at 6 months. Similarly, age (p=0.13), uterine volume (p=0.81) and fibroid dimeter (p=0.81) did not modify the need for reintervention.[117] The finding of no significant group difference in the rate of ovarian failure as measured by FSH >40 IU/L at 1 year after treatment (UAE vs. any surgery) was not modified by age less than 45 years or age of 45 years and older.[120]

The presence of a single fibroid (OR=6.21, 95% CI: 1.65 to 23.41) and small uterine volume (less than 500 cm^3) (OR=10.8, 95% CI: 1.25 to 93.36) were associated with higher risk of procedural failure. The risk for major complications (OR=5.68, 95% CI: 2.05 to 15.75) and high pain scores (higher than score of 5) (OR=1.97, 95% CI: 1.08 to 3.58) increased with each extra

vial of PVA used, though there was no significant association (p=NS) between high pain scores and uterine size, fibroid size, or total number of fibroids at 6 weeks after the procedure.[129]

A multivariate analysis indicated that compared to baseline, 24 months of treatment, higher number of fibroids was associated with lower risk of poor sexual function (OR=0.69, 95% CI: 0.51 to 0.94); while the presence of a comorbid condition was associated with an increased risk of a worse sexual function (OR=3.2, 95% CI: 1.38 to 7.41).[125]

Destructive procedures

A study comparing radio-frequency fibroid ablation to high-intensity focused ultrasound examined outcomes across groups by fibroid characteristic (fibroid blood supply and size).[51] The rate of complete ablation was significantly different between groups with different grades of supply. The radiofrequency ablation technical success rate was 89.3 percent versus 54.2 percent among individuals with Grade II blood supply (direct vessels to fibroid readily visualized). No difference was seen in within groups with no clear blood supply or widespread "halo" like blood supply; however the size of this trial was too small for meaningful assessment of true effect modification (total n = 100). Completeness of ablation was similar among the subgroups of patients with fibroid diameter between 2 cm and 4 cm, whereas the technical success for radiofrequency ablation was superior to HIFU in patients with fibroid diameters between 4.0 and 6.0 cm and between 6.0 and 8.0 cm ($p<0.05$)[51]

Surgical Interventions

An RCT with 181 women with fibroids who had been trying to conceive for at least 1 year without success, subdivided the women according to the location of the fibroid (i.e., submucous, intramural, subserosal) and randomized to myomectomy (laparoscopic myomectomy or HSM) or no surgery.[72] For women with subserosal or intramural fibroids, there was no significant difference in the pregnancy rate, comparing myomectomy with no treatment. For women with submucous fibroids, the group who underwent myomectomy had a greater pregnancy rate (40.4%) than those who did not undergo surgery (21.4%) ($p<0.05$).[72]

Summary of effect modification

Overall, there is insufficient evidence for women to choose one intervention over another based on individual characteristics or the characteristics of their fibroids. Too few studies have been adequately powered to determine within arms if one subgroup or another has superior outcomes within a treatment. Such information is required as a first step towards using individual characteristics to inform treatment choice.

Key Question 3. Risk of uterine sarcoma

KQ 3 Key Points

- Surgery for fibroids will reveal presence of a leiomyosarcoma in 3 to 10 women among every 10,000 procedures.
- Risk of dissemination is therefore 1 in 1,000 to 3,333 surgeries or 0.03 to 0.10 percent.

Overview

Risk of fragmenting and then releasing, or disseminating uterine sarcoma into the pelvic cavity is at the heart of the FDA and professional organizations concerns about power morcellation. The defining component of this risk is determining how likely it is that a surgeon who anticipates s/he is operating for benign disease will encounter a mass believed to be a fibroid that is actually a sarcoma. To address KQ 3 we pursued evidence in the literature to estimate the prevalence of uterine leiomyosarcoma among women treated for uterine fibroids.

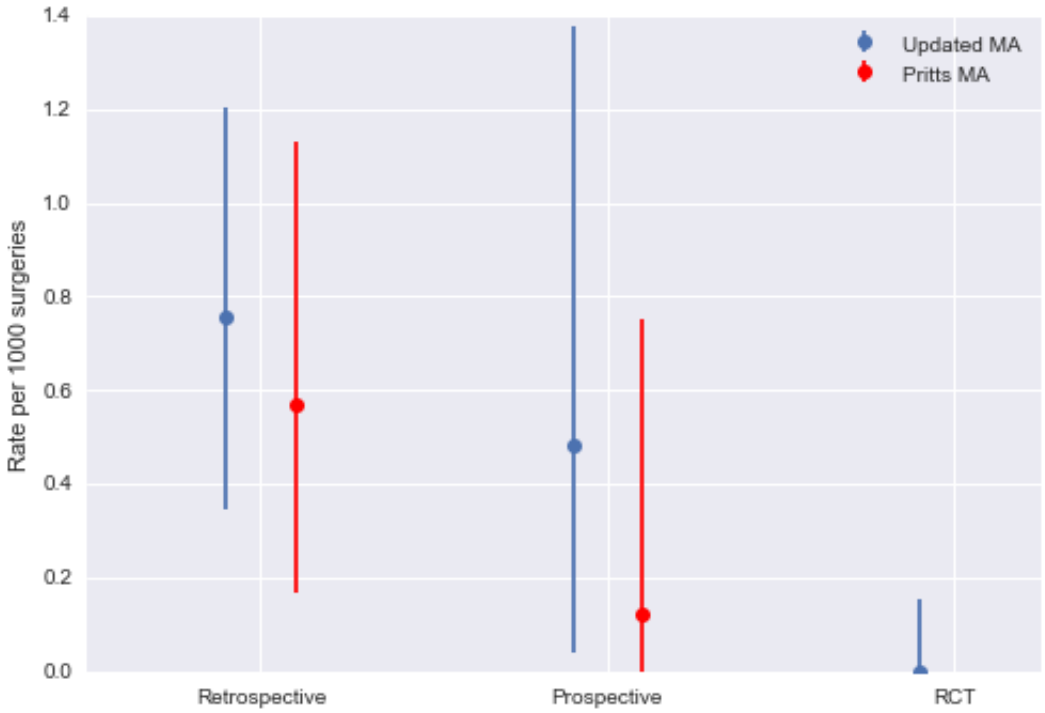
Description of Studies

We sought literature from studies of myomectomy or hysterectomy for presumed benign disease that included histopathologic analysis of all excised fibroid specimens. In the course of our work, Elizabeth Pritts and her colleagues published such an estimate using a similar approach, with a stated aim to estimate the prevalence of occult leiomyosarcoma at time of treatment for presumed benign tumors (fibroids).[18] We confirmed our search method included their articles and then updated their search using similar eligibility criteria to identify papers published since the end of their inclusion period in 2014. We retrieved 539 records and used dual review and prespecified criteria to screen for eligibility. In addition to the 133 unique studies included in the prior analysis, we identified 14 additional studies.[148-161] All were retrospective cohort studies[148-150,152-161] except for one population-based cohort study[151] (Appendix E).

Detailed Synthesis

The risk of sarcoma dissemination via morcellation of fibroids is immutably linked to the probability that there is sarcoma in what appears to be a fibroid at the time of surgery. Leiomyosarcoma is rare, an average of 1,600 new cases occur in the United States each year.[162] The Pritts analysis extracted data from 133 publications including 30,193 women.[18] The 14 new papers included substantially more women, contributing 91,294 women and bringing the total to data from 121,487 surgeries (Figure 8). Following methods described in Pritts et al., 2015[18] we fit a binomial random effects model to update the estimate of prevalence of leiomyosarcoma and achieved good model fit. The point estimate is a prevalence of 0.07 percent (95% CrI: 0.03 to 0.10).

Figure 8. Estimate of prevalence of leiomyosarcoma



Summary

The literature investigating the prevalence of sarcoma in presumed fibroids has grown rapidly and this continues to enhance risk estimates. Overall 3 to 10 women in every 10,000 who have surgery for fibroids may be found to have a sarcoma. Actual rates of dissemination that result in a fragment becoming a cancer implant leading to disseminated disease are more difficult to estimate. Nonetheless the risk of dissemination, based on size of the literature and precision of the estimates would not be expected to be higher than 0.10 percent for a population of women having fibroids surgery because it cannot exceed the risk that a tumor is present.

Key Question 4. Does risk of sarcoma dissemination differ by patient or fibroid characteristics or surgical approach to morcellation?

KQ 4 Key Points

- Survival time for women with uterine sarcoma, for whom power morcellation was used, compared to survival of women for whom sharp morcellation with a scalpel was used to assist removal of the surgical specimen, have similar survival.
- Survival time for women among whom the uterus was removed intact (because of known sarcoma or surgeon's preference) have similar survival times to both forms of morcellation.
- Uterine sarcoma has high mortality and the fact or method of morcellation is not associated with overall lethality of the disease.

Description of Studies

Sixteen studies provided data about disease progression and vital status for women who had a uterine sarcoma identified at the time of an initial surgery and for whom the method of removal of the surgical specimens was known and survival time data could be extracted.[157,159,160,163-175] These studies contributed data to compare survival time based on use of power morcellation, scalpel morcellation, or no morcellation. The research was conducted in 11 different countries, including five from the United States. The largest were from Taiwan and Korea. The majority identified baseline surgical data and outcomes after the events had occurred or relied on prospective registries and were able to provide followup for participants present at baseline. These studies included 196 women with sarcoma and the time of their initial surgeries ranges from the 1980s through 2014. This overlaps well with the period of growth in minimally invasive surgery for fibroids and with the use of power morcellation.

One additional study contained information about overall survival, morcellation approach, and characteristics of the women with sarcoma with only figures and no numeric data that could be extracted for counts.[176] These 17 publications[157,159,160,163-176] were reviewed for information about whether individual characteristics of the women or presumed fibroid status helped to identify those most at risk of harm. Similar to KQ 2, we sought evidence that investigated effect modification by factors such as age, menopausal status, imaging characteristics, which can be known before surgery and have potential to inform decision about surgical approach.

Detailed Synthesis

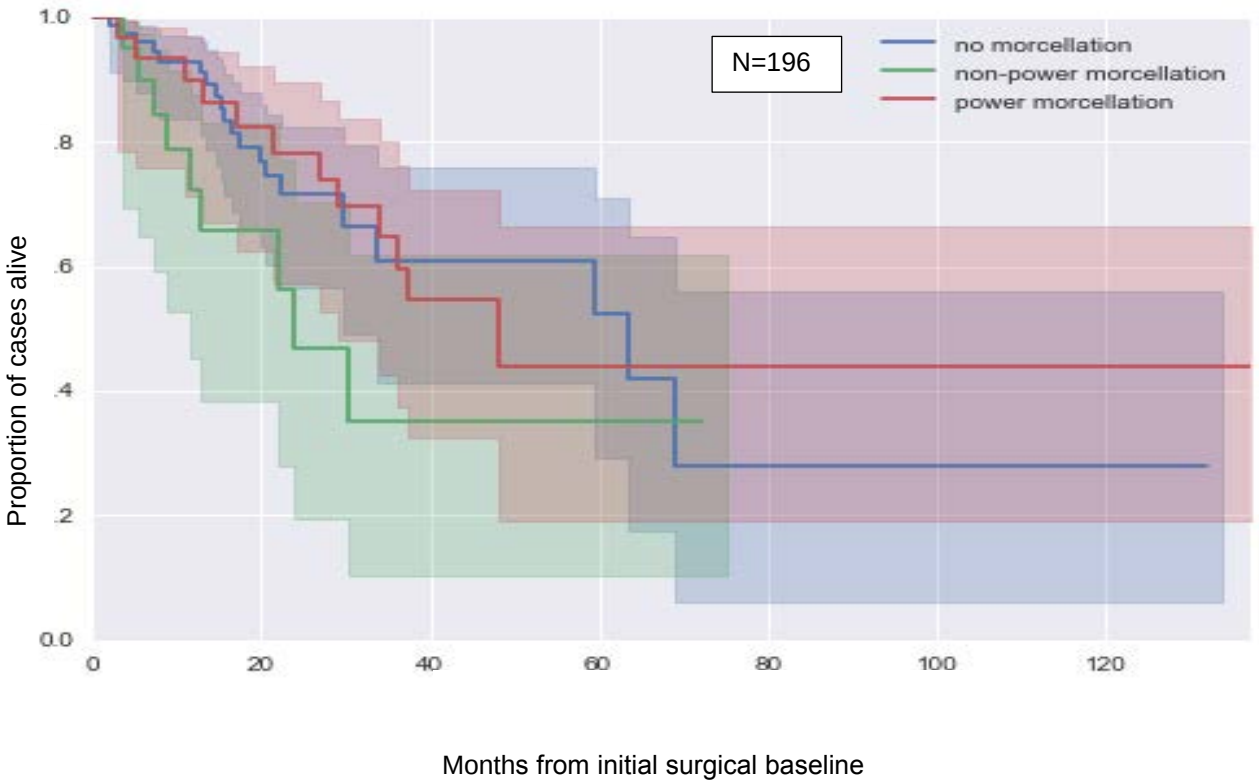
Our purpose for this aim was to determine if sarcoma dissemination was influenced by method of morcellation and to compare this with no use of morcellation while also assessing characteristics of patients and fibroids that might be associated with risk of dissemination. This is a separate question from the risk of having a sarcoma when surgeons believe they are operating on a fibroid discussed within KQ 3 and from the factors that determine that risk. Risk of sarcoma dissemination is more difficult to define than risk of presence of sarcoma.

If we consider the initial surgery as baseline, in most cases the diagnosis of leiomyosarcoma was not made until after the surgery at the time of assessment of the pathology specimen from what was believed to be a benign surgical case. Post hoc diagnosis is uniformly true for cases

with use of power morcellation. Surgeons do not use the technique if cancer is suspected. Thus the pathology review, and typically a related tumor board clinical conference, establishes the diagnosis of leiomyosarcoma. However it cannot establish what was present in the abdomen or pelvis as gross or microscopic lesions at baseline. It is plausible that in some instances disseminated disease existed at baseline and was not seen, especially with vaginal or minimally invasive approaches, but also possible with abdominal surgeries. Even with near term imaging such as MRI or CT scan, or with a proximate repeat surgery for staging of the cancer, it is not possible to determine if there are implants on adjacent or distance tissue how they came to be at that location as there is not currently a method to "tag" the origin of disseminated tissue.

As a result, stage of disease, progression of disease, and survival with or without persistent and recurrent cancer become surrogates for the fact of cancer spread whether or not the surgical approach or the tumor are the underlying mechanisms of spread. If, as feared, dissemination is in essence provided by use of power morcellation and both visible and microscopic particles are spread in the pelvis and abdomen by the device or by presence of fragments in irrigation fluid or contact with contaminated instruments that harbor pieces of tumor, we would hypothesize that stage and survival would be worse for those in whom leiomyosarcomas were removed by power morcellation compared to sharp morcellation and that both of these would be inferior to no breach of the integrity of the uterus by removing the uterus and tumor intact. Kaplan-Meier curves portray this data as the proportion of women with sarcoma who are alive at estimated time points based on follow-up interval. The figure below (Figure 9) is representative of the model output with the shaded areas indicating the 95% credible bounds around the respective categories of no use of morcellation, sharp morcellation and power morcellation.

Figure 9. Survival after surgical intervention for leiomyosarcoma by morcellation approach



By five years of followup (60 months), which is a typical cancer survivorship window often used as a surrogate for cure, the three approaches cannot be distinguished. At earlier periods, no morcellation and power morcellation are similar and in some windows, sharp morcellation (non-power) appears to have worse outcomes based on having the steepest drop in survival in the first 36 months and some brief periods in which confidence bounds do not overlap. A conservative interpretation of this aggregate analysis is that there is not a statistical difference in outcomes that is determined by the surgical approach used to remove the uterus or fibroids. The analysis does not rule out that power morcellation contributes to dissemination.

The final paper for KQ 4 that did not report individual level data that could be extracted had the second largest number of sarcoma cases and was conducted in France. They identified 53 patients with uterine sarcoma and found rates of pelvic recurrence did not differ by use of morcellation at three or six months of follow-up with comparable disease-free survival rates in both groups.[176] Combined our Bayesian meta-analysis and this data concur with the findings of a review and lifetable analysis recently published by Pritts and colleagues[177] that do not document a statistically meaningful disadvantage to morcellation when aggregate data are used to calculate survival.

Within this literature, few authors had sufficient number of cases to address differences in risk of dissemination or survival by other characteristics of the women found to have leiomyosarcoma at the time of surgery for presumed fibroids. If we consider only those studies with more than 10 cases with sharp or power morcellation, only five publications with total size of 15 to 56 participants have potential to contribute information.[165,173-176] Two do not provide adjusted multivariable models or stratification by characteristics other than operative approach.[165,178] None report assessment of effect modification by any trait other than surgical approach to removal of the uterus or fibroids.

Characteristics reported not to confound the association between risk of dissemination and outcome in multivariable time-to-event models included: age,[174,175] menopausal status,[174,175] adjuvant treatment including radiotherapy,[174,175] and BMI.[174] The publications authored by Perri and Park[174,175] both report only surgical approach grouped as total abdominal hysterectomy or other approaches with any morcellation or breech of the tumor capsule, significantly influenced outcomes. Lin and colleagues adjusted for age, tumor size, and mitotic count, but including these covariates in the model did not meaningfully change estimates.[173] As a result this literature lacks information to identify those most likely to have a more aggressive course of disease beyond pathology features of tumor differentiation and stage. This is not an unexpected outcome since uterine sarcoma is rare and power is limited. It is helpful however that larger studies do not find other characteristics act as confounders. This implies that our aggregate estimate and those of others are not likely to be seriously confounded by commonly measured clinical factors.

In summary this literature provides data to indicate that method of morcellation is not a dominant determinant of outcomes and that even those who have hysterectomy with removal of the uterus intact have comparable outcomes over long-term followup for survival.

Discussion

Key Findings

Strength of Evidence

We assessed the strength of evidence for medical, procedural, and surgical intervention effects on fibroid volume, uterine bleeding, and quality of life.

Expectant Management

Fourteen studies randomized 551 women with uterine fibroids to a no intervention arm.[36,38,49,60,68,71,72,80,86,91,92,102,109,112] One of these trials one was of good quality, five were fair, and eight were poor (Table 32). We assessed the strength of evidence for changes in fibroid volume or size (reported in nine studies), bleeding outcomes (reported in 11 studies), and quality of life (reported in four studies).

Table 32. Strength of evidence for expectant management effects on fibroid volume, bleeding, and quality of life: 14 studies (n=551)

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
Fibroid Volume							
9 studies, 9 arms 276 randomized	Low: 1 Moderate: 2 High: 6	High	Direct	Inconsistent	Precise	Not detected	Low
Bleeding							
11 studies, 11 arms 345 randomized	Low: 1 Moderate: 5 High: 5	High	Indirect	Inconsistent	Precise	Not detected	Low
Quality of Life							
4 studies, 4 arms, 104 randomized	Moderate: 1 High: 4	High	Direct	Consistent	Precise	Not detected	Low

Abbreviations: SOE=Strength of Evidence.

Medication

Of the 40 studies that assessed a medical intervention for management of uterine fibroids and included in this review, 32 reported changes in one or more prespecified outcomes for fibroid volume, uterine bleeding, or quality of life. We report the strength of evidence for GnRH treatment (Table 33), progesterone antagonist and selective receptor modulators (Table 34), and estrogren receptor agents (Table 35).

Table 33. Strength of evidence for GnRH treatment effects on fibroid volume, bleeding, and quality of life

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
Fibroid Volume							
10 studies, 16 arms, 415	Low: 1 Moderate: 1	High	Direct	Consistent	Precise	Not detected	Moderate

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
randomized	High: 8						
Bleeding							
12 studies, 17 arms, 547 randomized	Moderate: 3 High: 9	High	Direct	Consistent	Precise	Not detected	Moderate
Quality of Life							
1 study, 2 arms, 110 randomized	High: 1	High	Direct	Unknown	Unknown	Not suspected	Insufficient

Abbreviations: SOE=Strength of Evidence

Table 34. Strength of evidence for progesterone antagonist and selective receptor modulators treatment effects on fibroid volume, bleeding, and quality of life

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
Fibroid Volume							
Mifepristone (5 studies, 9 arms, 596 randomized)	Moderate: 3 High: 2	Medium	Direct	Consistent	Precise	Not detected	Moderate
Ulipristal (4 studies, 8 arms, 700 randomized)	Moderate: 2 High: 2	High	Direct	Consistent	Precise	Not detected	Moderate
LNG-IUD *Fibroid volume not reported*	NA	NA	NA	NA	NA	NA	Insufficient
Bleeding							
Mifepristone (6 studies, 11 arms, 668 randomized)	Moderate: 4 High: 2	Medium	Direct	Consistent	Precise	Not detected	Moderate
Ulipristal (3 studies, 5 arms, 688 randomized)	Moderate: 2 High: 1	High	Indirect	Consistent	Precise	Not detected	Moderate.
LNG-IUD (1 study, 1 arm, 30 randomized)	High: 1	High	Direct	Unknown	Unknown	Not suspected	Insufficient
Quality of Life							
Mifepristone (4 studies, 6 arms, 374 randomized)	Moderate: 2 High: 2	High	Direct	Consistent	Precise	Not detected	Moderate.
Ulipristal (3 studies, 5 arms, 704 randomized)	Moderate: 2 High: 2	High	Direct	Consistent	Precise	Not detected	Moderate
LNG-IUD *Quality of life not reported*	NA	NA	NA	NA	NA	NA	Insufficient

Abbreviations: LNG-IUD: levonorgestrel intrauterine device; NA: not applicable; SOE=Strength of Evidence

Table 35. Strength of evidence for estrogen receptor agents treatment effects on fibroid volume, bleeding, and quality of life

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
Fibroid Volume							
3 studies, 4 arms, 103 randomized	Moderate: 2 High: 1	Medium	Direct	Inconsistent	Imprecise	Not detected	Low
Bleeding							
3 studies, 4 arms, 104 randomized	Moderate: 2 High: 1	Medium	Indirect	Consistent	Imprecise	Not detected	Low
Quality of Life							
Quality of life not reported	NA	NA	NA	NA	NA	NA	Insufficient

Abbreviations: SOE=Strength of Evidence; NA=not applicable

Procedures

Table 36. Strength of evidence for uterine artery occlusion effects on fibroid volume, bleeding, and quality of life

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
Fibroid Volume							
11 studies, 21 arms, 708 randomized	Low: 4 Moderate: 4 High: 3	Low	Direct	Consistent	Precise	Not detected	High
Bleeding							
9 studies, 16 arms, 438 randomized	Low: 1 Moderate: 4 High: 4	Medium	Indirect	Inconsistent	Precise	Not detected	Low
Quality of Life							
7 studies, 11 arms, 493 randomized	Low: 2 Moderate: 4 High: 1	Medium	Direct	Consistent	Precise	Not detected	Moderate

Abbreviations: SOE=Strength of Evidence; NA: not applicable

Table 37. Strength of evidence for HIFU or fibroid ablation effects on fibroid volume, bleeding, and quality of life

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
Fibroid Volume							
HIFU (3 studies, 6 arms, 153 randomized)	High: 3	High	Direct	Consistent	Precise	Not detected	Low
Fibroid Ablation *Fibroid volume not reported*	NA	NA	NA	NA	NA	NA	Insufficient
Bleeding							

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
HIFU *Bleeding outcome not reported*	NA	NA	NA	NA	NA	NA	Insufficient
Fibroid Ablation *Bleeding outcome not reported*	NA	NA	NA	NA	NA	NA	Insufficient
Quality of Life							
HIFU *Quality of life not reported*	NA	NA	NA	NA	NA	NA	Insufficient
Fibroid Ablation *Quality of life not reported*	NA	NA	NA	NA	NA	NA	Insufficient

Abbreviations: SOE=Strength of Evidence; NA=not applicable; **Notes:** HIFU: 5 studies, 363 patients[25,30,32,39,51] Fibroid Ablation: 2 studies, 76 patients.[29,51]

Surgery

Table 38. Strength of evidence for surgery effects on fibroid volume, bleeding, and quality of life

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
Fibroid Volume							
Endometrial ablation *Fibroid volume not reported*	NA	NA	NA	NA	NA	NA	NA
Myomectomy *Fibroid volume not reported*	NA	NA	NA	NA	NA	NA	NA
Hysterectomy *Fibroid volume not reported*	NA	NA	NA	NA	NA	NA	NA
Bleeding							
Endometrial ablation (1 study, 2 arms, 96 randomized)	Moderate: 1	Medium	Direct	Unknown	Unknown	Not suspected	Insufficient.
Myomectomy *Bleeding outcomes not reported*	NA	NA	NA	NA	NA	NA	Insufficient
Hysterectomy (1 study, 1 arm, 30 randomized)	High:1	High	Direct	Unknown	Unknown	Not suspected	Insufficient
Quality of Life							
Endometrial ablation (1 study, 2 arms, 96 randomized)	Moderate: 1	Medium	Direct	Unknown	Unknown	Not suspected	Insufficient
Myomectomy (2 studies, 2 arms, 239	Moderate: 1 High: 1	High	Direct	Consistent	Precise	Not detected	Moderate

Studies	Risk of Bias	Study Limitations	Directness	Consistency	Precision	Reporting Bias	SOE *Findings*
randomized)							
Hysterectomy (2 studies, 2 arms, 204 randomized)	High: 2	Medium	Direct	Consistent	Precise	Not detected	Low

Abbreviations: SOE=Strength of Evidence; NA: not applicable; **Notes:** Myomectomy: 19 studies; [29,34,39,40,44-46,50,54,55,59,64,66,72,74,77,93,97,104] Six studies of myomectomy reported harms only.[29,40,45,55,59,64] Hysterectomy: 14 studies[28,46,52,58,75,78,82-84,88,89,94,98,100] Seven studies of hysterectomy reported harms only (i.e., did not report final health outcomes for effectiveness).[28,58,83,88,89,94,98]

Findings in Relationship to What is Known

Existing Systematic Reviews

We searched for systematic reviews published between 2002 and 2015. We evaluated each for relevance to our Key Questions using the review PICOTS. We identified 23 systematic reviews of interventions to treat uterine fibroids (Appendix J).[135,179-200] The reviews addressed the following categories of interventions: medical (12 reviews), UAE (5 reviews), procedural (2 reviews), uterine sparing (1 review), and surgical (3 reviews). The reviews overall were characterized by small numbers of included studies and data on long-term outcomes including future fertility was limited. Harms were addressed in only a few reviews.

Existing Reviews of Medical Interventions

The medical interventions evaluated in the 12 medical systematic reviews included GnRH analogues in four reviews,[135,179,186,195] progesterone antagonists including mifepristone,[199] SERMs,[193] and progesterone-containing IUDs.[184,190,197,198] A single review analyzed studies of aromatase inhibitors[188] and tranexamic acid.[181]

GnRH analogues were evaluated in four reviews.[135,179,186,195] A Cochrane review of GnRH with add-back therapy assessed quality of life in 14 RCTs.[179] Add-back therapies included medroxyprogesterone, tibolone, raloxifene, estriol, ipriflavone, and conjugated estrogens. Tibolone was associated with an improved quality of life and add-back therapies of tibolone, estriol, and ipriflavone helped preserve bone mass, but the quality of evidence for these finding s was considered low.

Three reviews examined use of GnRH analogues as pre-medication prior to surgical procedures. Lethaby et al. summarized 20 RCTs that demonstrated preoperative GnRH agonist treatment reduced uterine volume and fibroid size and improved surgical bleeding outcomes.[135] Chen et al. analyzed data from three RCTs that compared GnRH versus no treatment or placebo prior to laparoscopic myomectomy.[195] GnRH significantly reduced intraoperative blood loss but did not shorten the operation time. Kamath et al. only found two studies that compared GnRH with placebo or no treatment in women with submucosal fibroids prior to hysteroscopic resection.[186] The primary outcome of symptom relief was inconclusive.

Progestogen-releasing intrauterine systems were evaluated in four systematic reviews.[184,190,197,198] A small Cochrane report of progestogens included only a single small study that compared the LNG-IUS to oral contraceptives and found significant reduction in blood loss for IUD users.[190] LNG-IUD was associated with reduced menstrual blood loss reported in three

other reviews that included few to no RCTs.[184,197,198] Women with fibroids may have higher device expulsion rates.[197]

A Cochrane review of SERMs used to treat leiomyoma only included three small RCTs.[193] All of the studies evaluated raloxifene but the evidence for the effectiveness in reducing fibroid size and improving clinical outcomes was inconclusive. An older systematic review of mifepristone included six pre-post studies.[199] Mifepristone was associated with a reduction in fibroid size and improvement in symptoms but there were no comparative studies in this review.

Another Cochrane review of aromatase inhibitors found only a single RCT comparing letrozole to GnRH agonist.[188] There were no statistically significant differences in fibroid volume after 12 weeks of treatment. A single review of tranexamic acid for management of menorrhagia due to fibroids noted that it may reduce perioperative blood loss during myomectomy.[181]

Our review documents effectiveness of GnRH agonists for reducing fibroid volume and improving bleeding outcomes and improved symptom status when combined with add-back therapy and provides comparative trial evidence for the effectiveness of mifepristone in fibroid size reduction and resolving bleeding problems.

Existing Reviews of Procedural Interventions

Two reviews evaluated MRI-guided focused ultrasound treatment of uterine fibroids.[185,189] These reviews did not include any RCTs; conclusions were from analysis of retrospective studies and case series. Outcomes assessed included symptom severity from UFS-QOL, subsequent pregnancy, and harms. MRgFUS treated women had an improved quality of life as assessed 6 months following treatment, future fertility was preserved, and procedure was well tolerated with only one serious adverse event of deep vein thrombosis reported. In contrast, the studies of MRgFUS (HIFU) included in this review (all RCTs) did not report pregnancy or other patient-centered outcomes, but focused on technical success.

Existing Reviews of UAE Interventions

Uterine artery embolization was evaluated in five systematic reviews.[180,187,191,192,194] Four of these reviews reported on comparative studies of UAE versus surgical treatments for uterine fibroids.[180,191,192,194] More favorable short-term outcomes, including less blood loss[194] and a quicker return to usual activities,[194] were noted for UAE compared to surgery. The risk of major complications was less with UAE[191,192] but the procedure is associated with higher rates for reintervention reported in three systematic reviews.[191,192,194] There were no differences in patient satisfaction after two and five years[180] and long-term quality of life was comparable.[180,194] Data for live birth outcomes following UAE were limited.[180] One review that examined comparative studies of UAE using different embolic agents did not find any evidence of superiority of any particular agent.[187] Our findings on patient satisfaction and quality of life outcomes following embolization in comparison with surgical treatments were comparable to what has been previously reported.

Existing Reviews of Uterine-Sparing Interventions

A single systematic review of five RCTs in premenopausal women who wanted to preserve their uterus reported comparisons between UAE with myomectomy and laparoscopic uterine artery occlusion.[183] Patient satisfaction was better for UAE and myomectomy compared to laparoscopic uterine artery occlusion. Limited evidence was available for fertility and pregnancy

outcomes. Our review also had limited evidence for reproductive outcomes following uterine sparing procedures.

Existing Reviews of Surgical Interventions

Three systematic reviews evaluated surgical treatments for uterine fibroids.[182,196,200] A large review of 34 RCTs compared vaginal, abdominal, and/or laparoscopic assisted hysterectomies in women with benign disease, although only six of these trials specifically addressed surgical treatment for uterine fibroids. Vaginal hysterectomy was associated with a quicker return to usual activities and fewer infections compared to abdominal hysterectomy.[200] A review of nine RCTs comparing laparoscopic or hysteroscopic versus open myomectomy found improved short-term outcomes (less postoperative pain and shorter hospitalization) for laparoscopic procedures.[182] Another small review of four RCTs noted a significantly shorter operation time for vaginal myomectomy compared to laparoscopic. Data was not available for long-term outcomes in these reviews. This review also reports higher patient satisfaction and shorter recovery time for vaginal hysterectomy compared to abdominal hysterectomy.

Applicability

Overall, our findings are widely applicable to the general population of women seeking treatment for uterine fibroids. For KQs 1 and 2 we set inclusion criteria for this review to women of any age with uterine fibroids with patient outcome data beyond intermediate outcomes only. We excluded studies in pregnant women, and restricted our synthesis to include only treatments currently available in the United States. Over 40 percent of the studies were conducted in European countries and another 27 percent were conducted in the United States or Canada. The interventions themselves were selected to be comparable so that the results reported in this review are expected to apply to women with fibroids in the United States.

Evaluation of expectant management was not an explicit aim of any trial. Fourteen studies with placebo arms or no treatment arms that included 308 women served as a surrogate. This population is not an ideal substitute as participants in the trials presumably hoped to receive active treatment and may report their status differently than women willing to be randomized to watchful waiting. This could restrict applicability but we have included since 12 of the 14 studies included a plausible level of masking of participants such that they would be unlikely to know if they were on an active agent. Two pharmaceutical management trials include an arm with an agent not available in the United States, one including tibolone[102] and another asoprisnil.[68]

Medical management of fibroids was assessed in over 2,200 predominately premenopausal women from 40 studies (13 industry-sponsored and 11 conducted in the United States). Procedures, including uterine artery embolization, high intensity focused and magnetic resonance-guided focused ultrasound and ablation were evaluated in 25 studies including almost 2,000 women. Surgical studies evaluated hysterectomy, myomectomy, and ablation in over 3,000 women. Although none of these studies were conducted in the United States, the surgical techniques described are comparable and the comparators are procedures widely available to women in the United States.

While there are limitations in the literature as discussed below, the information that is available from these trials is relevant to contemporary practice. In summary, this review is generally applicable to women in the United States seeking one of the many treatment choices currently available for fibroids.

Implications for Clinical and Policy Decisionmaking

Available evidence from randomized clinical trials about the effectiveness of interventions is predominantly restricted to understanding outcomes of specific interventions and not comparisons among them. Therefore, this literature predominantly provides evidence that an intervention delivers certain desired outcomes but not how those outcomes vary across types of intervention. While it is helpful to know that confidence in particular medications, procedures, or surgeries is not misplaced, it is not sufficient to fully inform choice among the options or to drive decisions about coverage by health plans.

Some implications for clinical care and other decisionmaking can be highlighted. Women with fibroids and symptoms typically have time to make decisions and the process need not feel emergent or rushed. This presumes that a patient's medical condition is not acutely emergent, an exceptionally small minority of those seeking care. More typically symptoms are persistent and troubling but not life threatening. In these instances, RCT data from placebo groups shows that fibroids do not grow substantially over a period of time that averaged seven months, neither did bleeding pattern substantially worsen.

Several medications show benefit for reducing the size of fibroids, improving bleeding, and reducing symptoms. These include GnRH agonists, ulipristal, and agents that act on estrogen receptors. Mifepristone provided stabilizing effects on the size of fibroids (no growth) with similar improvement in symptoms. In a single study, among women randomized to have an immediate hysterectomy or to defer hysterectomy and be treated with a GnRH agonist, 61 percent did not have surgery over a period of three years of follow-up, suggesting a meaningful proportion of even very symptomatic women who wish to pursue medical intervention may avoid surgical intervention.[100] These medical management options are likely under-utilized in clinical practice and care guidelines might more directly address instances that merit consideration. Certainly all women with fibroids should at minimum be aware medications for management of fibroids exists. We also note that these interventions are not compatible with and in some cases prevent pregnancy, while in others contraception is required.

Procedures also deliver the expected results. Uterine artery occlusion reduces the size of fibroids, has modest to minimal effects on bleeding, improves pressure and bulk symptoms, and improves quality of life. High intensity focused ultrasound has fewer trials but they provide evidence of effectiveness for reducing size with gaps in findings about bleeding, symptoms, and quality of life and durability of improvements. This poses challenges for determining if procedures should be covered or if healthcare systems should make the requisite investments to have the required professional expertise and equipment available to perform procedures. Other interventions are more rarely used or not included in the literature but important. These are discussed in future research needs.

Surgeries are most studied. Hysterectomy remains definitive treatment. Less invasive hysterectomy options (transvaginal and laparoscopic compared to an abdominal incision) have superior patient satisfaction and shorter recovery. Overall harms did not differ in ways that would warrant consideration of harms driving a clinical choice. Myomectomy follows the same pattern, less invasive approaches had less impact on women's lives and harms were equivalent. It is notable that evidence suggests only intervention for submucous fibroids (those in the uterine cavity), as opposed to other more common locations, improve subsequent pregnancy outcomes. Women are at times advised to have myomectomy to improve reproductive outcomes and this review, as well as a related recent Cochrane review of randomized trials of myomectomy,[201] suggests this is not the case.

Few direct comparisons across the categories of interventions are available inform care. Two small studies of fair quality compared UAE to hysterectomy.[44,124] Three larger studies, including the 28-site EMMY trial compared UAE to hysterectomy.[52,78,82] As a group these studies provide a good case for why more trials making direct comparisons are needed. The studies find UAE provided similar symptom relief, quality of life, and risk of fibroid recurrence (the latter compared to myomectomy). UAE had shorter recovery and lower transfusion risk than both myomectomy and hysterectomy. However, women with UAE were more likely to have future procedures but even this was a comparatively small proportion. In the high quality study with longest followup at five years, fewer than one third of women assigned to UAE required additional intervention, emphasizing that over two-thirds avoided surgery.[78] Detailed information like this can help women weigh options more fully from an individual perspective. In this way comparative effectiveness data will improve care because it allows individual priorities, for instance for less invasive procedure or more definitive intervention to be acted on with confidence.

Likely no topic in gynecologic surgery, other than abortion ethics, has stirred as much public controversy as recent concerns about use of power morcellators in the care of women with fibroids. The concern pivots on an essential question about risk that we have updated from the last estimate in the published literature. The bedrock question on which all other considerations rest is: What is the expected risk of planning a surgery for uterine fibroids and unintentionally encountering a uterine sarcoma? While women and their physicians alike would like this number to be zero it is not, but it is a small risk. The point estimate of prevalence is 0.07 percent (95%CrI: 0.03 to 0.10). Between three to 10 women in 10,000 who have surgery for a fibroid may have a sarcoma. We fear this outcome because overall sarcomas have poor outcomes with an average survival of 36 percent at five years if cancer is present in the abdomen and pelvis and not isolated to the uterus.[202]

Level of acceptable risk is variable, contextual, and highly individual. In our meta-analysis of 16 studies that provide data about use of morcellation in three categories: none, scalpel, or power, we find that power morcellation *per se* is not a definitive determinant of dissemination and death from sarcoma. Survival curves cannot be easily visually distinguished between the two approaches to morcellation, and with statistical confidence bounds considered neither morcellation method is definitively worse than hysterectomy without morcellation. Combined this suggests sarcoma is often a deadly cancer and that surgical approach, including use or no use of morcellation, is not the dominant factor determining outcomes. Available data cannot be used to implicate power morcellation as an independent cause of poor outcomes. This aligns with recent estimates in the literature.[177] It also reflects the concept that hematogenous spread, meaning through the blood stream, is a key factor associated with lethality and that more than half of women with uterine sarcomas present with distant metastasis before recurrent cancer in the pelvis, and most progress to higher stage disease regardless of order of spread.[203,204] Unfortunately the literature does not speak to characteristics of the individual or characteristics revealed by imaging of her fibroids that can discriminate those at high risk from those with lower risk. While we know risk increases with age, age is neither sensitive nor specific given such a rare condition.

Taken together these findings suggest a ban on morcellation requires at least ongoing investigation with expanded data. Some have cautiously argued such as ban could result in an increase in harms to women.[205,206] Is it prudent with a known sarcoma to avoid breaching the mass and to aim for intact removal? Of course. Might containment systems in which

morcellation occurs within a closed bag-like system help? Potentially. Is it wise to perhaps advise older women that they are at increased risk of sarcoma and if childbearing is completed may wish to consider intact removal by hysterectomy? Perhaps, but the magnitude of risk averted is unknown. In each of these instances we have outstripped the evidence and guidance reverts to expert opinion. In discussion of future research we consider what data may better inform clinical and policy guidance.

Taken in total, women and care providers now have more and higher quality evidence of effectiveness than a decade ago, and the literature addresses multiple types of intervention in each of the categories of medication, procedural, and surgical management. Individual women should have access to this information to inform their decisions and factual estimates of outcomes should be used to guide the consenting process. Nonetheless, we need to continue to pursue questions about care trajectories, comparisons across categories of intervention and longer-term followup to best guide care and policy.

Limitations of the Systematic Review Process

Methodologic choices constrain the findings of this report. We chose to focus on publications in the English-language literature, to restrict to randomized clinical trials, and to review only those studies that included at least on intervention that is available in the United States. Similar reviews have documented in the past that language restrictions have a negligible effect on estimates of effectiveness.[207,208] This is especially true for the topic of fibroids because the fibroid research community is small. Our technical expert panel and authors are familiar with prior and ongoing work and helped assure relevant studies have not been overlooked. Restricting to trials allowed us to sharply focus on proof of effectiveness. Because all individuals whose outcomes were assessed in these studies were randomly assigned to the intervention received, provider and patient biases in intervention choice are reduced and risk of confounding, that is difficult to fully assess or adjust for in cohorts, is minimized. Reduced risk of bias in assignment in trials allows aggregation and summary of the findings by study arm, as we have done in summaries and tables in this report. This approach provides a clearer picture of the expected outcomes and gaps in knowledge about specific interventions. Considering each possible combination of intervention arms and reporting per combinations of interventions fractionates this literature into very small groupings in which concordant and discordant findings about outcomes are more easily obscured.

We have used meta-analysis techniques to help focus on what we know with some precision and what knowledge remains elusive. Our analysis of subsequent intervention after a first intervention could be biased by the types of studies that reported this data; however, in general they were higher quality trials with longer followup. Nonetheless, subsequent care, even in longer follow-up, often represented a small number of women and our analysis can only broadly address probability of a next intervention by type. For meta-estimates related to morcellation risk, available evidence, based on pathology specimens for estimating presence of sarcoma in a mass believed to be a fibroid is accruing and will likely continue to do so through and past the production of this report. Our estimates and that of Pritts and colleagues[18] find that the estimates are lower in data from more contemporary prospective cohorts of women having surgery. This suggests some inaccuracies in retrospectively collected data even when pathology specimen banks are used to index a full population of surgical patients. This risk of inaccuracy is especially true in understanding and estimating the potential that morcellation method influences survival when a woman is found to have a sarcoma that was believed to be a fibroid. All sources of

information, including women with fibroids removed intact at hysterectomy must be included in order to accurately capture risk of this rare outcome. Focusing only on disease progression rate and risk of death among those with use of power morcellation fundamentally misrepresents the true comparison. We have taken this approach for this review; however, such comparisons will only be complete and more robust for informing care when the literature contains more longitudinal data with common metrics.

Focusing on interventions available in the United States, and excluding those that cannot be obtained here could neglect a promising intervention but does restrict the report to data that is of immediate value to women and their care providers who must make decisions among available options. We have included interventions that are not widely available in the United States such as high frequency ultrasound ablation and operative thermal ablation, so in the strictest sense of applicability, some women live in locations, or have access to a limited group of providers or face limitations of insurance coverage that may restrict the availability of some options.

Limitations of the Evidence Base

While the literature about the effectiveness of uterine fibroids treatment has grown from 35 randomized clinical trials available in 2007, to 90 unique trials, with 109 publications included in this report, significant gaps in knowledge persist. Across all studies, the 90 included RCTs, with 97 unique intervention arms, enrolled only 8,118 women. Individual studies were often small and powered to address only a single continuous outcome such as hematocrit or score on a quality of life scale.

Our causal framework was created to reflect the outcomes that matter to women when making decisions. The available literature has substantial gaps in collecting this information as indicated by the number of studies that addressed each of our eight primary outcomes:

- Fibroid characteristics (e.g. change in size, number, volume): 51
- Symptoms status (e.g. bleeding, pain, bulk symptoms): 51
- Sexual function: 10
- Quality of life and satisfaction with outcomes: 8
- Desired fertility status: 1
- Pregnancy outcomes: 8
- Fibroid recurrence: 5
- Subsequent treatment for fibroids: 19

Little continuity exists in approaches to measuring outcomes and use of unvalidated measures is common. Most postprocedural studies focused on perioperative outcomes, although a small minority recorded long-term outcomes, with one study reporting on 5-year outcomes. The literature is further restricted in its ability to answer questions of immediate relevance to the management of uterine fibroids because only a small number of studies compared different types of fibroid management. Although several studies compared different types of hysterectomy, myomectomy, or pharmaceutical management, only 18 studies compared treatment from substantively different categories of intervention.

Even when data is combined across studies for a particular intervention, risk of serious rare harms cannot be fully assessed. This is not a comparable shortcoming for all the categories of intervention because the larger literature on surgical and medical interventions captures many of the “general risks,” for instance the risk of postoperative hemorrhage after hysterectomy or adverse drug reactions to a specific drug formulation. Relative lack of harms data is more concerning for fibroid-specific interventions such as UAE, methods to ablate fibroids, and

myomectomy because there is no broader literature to turn to outside this review that originates within clinical trials though cohort and surveillance data can provide insight.

In many instances ability to synthesize evidence across studies is absent, weak because of biased collection methods (e.g. assessors not blind to intervention), difficult to aggregate across studies because of use of different metrics, or the studies did not have adequate power or follow-up time to assess a key outcome that would ideally be measured.

Paucity of "similar" articles (populations, settings, patient characteristics, and outcomes measured) also precludes efforts to pool data about characteristics of the study populations as they contribute to predicting outcomes and no studies were appropriately powered to understand whether specific groups of patients, such as those closer to menopause or with a specific symptom pattern have outcomes that are modified by those characteristics.

Overall quality of the literature is improving over time but we have not arrived. Among 90 trials, 15 were good quality, 27 were fair quality, and 48 were poor quality. Secular trends for improvement in trial methods do not explain poor quality. Some studies of good quality are older, and some studies of poor quality are very recent. Lastly, a disappointing lack of direct comparisons means this review is hindered in providing summaries with data to help a woman or her care provider make an evidence-driven selection among choices in the context of the patients' priorities.

Research Recommendations

Key components of study design, analysis, and reporting remain the leading weaknesses of the literature for each topic addressed in this review. Overall, the literature identified is limited by the following gaps and problems. Future research should aim to remediate these concerns:

Ability To Assess Internal and External Validity. Key characteristics of populations studied (e.g., race/ethnicity, reproductive history) and detailed operational definitions of inclusion and exclusion criteria are not reported consistently. Furthermore, the dominance of European literature means that we cannot assume that processes of care and outcomes will be similar to those in the United States. Moreover, practice variation and outcomes have been shown in other areas of research such as cardiac care to have substantial variability within the United States and even within individual states and facilities. We see no reason to believe that such variation is not also at work in the care of fibroids; more and better information from U.S. studies is required to advance our understanding about this important women's health issue.

Study Populations of Adequate Size for Assessing Key Outcomes. The small size of most of the included trials, which averaged fewer than 100 participants, stymies ability to understand modifiers of outcomes that could be extremely relevant to clinical decision making. Though most trials reported power calculations, calculations were often linked to intermediate outcomes such as blood loss at surgery, length of hospital stay, or bleeding pattern at 3 months of medical therapy. Even with power calculations, the sizes of the samples precluded having adequate numbers of participants for the types of answers that are needed to inform women and their care providers about the critical questions raised for this report. Future research would be better able to provide such answers if funding agencies supported studies of adequate size to answer questions about resolution of symptoms, satisfaction with outcomes, recurrence or growth of fibroids, and further care needs at time horizons of a year and longer.

Standard Nomenclature and Validated Measures. To advance knowledge, investigators need to adopt common classifications across the whole spectrum of operational definitions required for research. Several deficiencies handicap our ability to compare interventions and

populations or aggregate data to estimate effect size and outcome probabilities. Three shortcomings are especially problematic: (1) failure to define operationally details such as fibroid type or position in the uterus; (2) reliance on clinical measures such as estimated blood loss from operative reports or febrile morbidity from nursing notes as endpoints; and (3) use of ad hoc measures of outcome that lack validity and reliability data (e.g., intuitively derived approaches to collecting data about success in controlling bleeding or altering bleeding patterns).

Analysis Methods Matched to the Outcomes of Interest. Follow-up data that investigate topics such as time to return to work, maintenance of symptom control, recurrence of fibroids, subsequent surgery, and fertility and pregnancy outcomes should be addressed with analysis methods that explicitly incorporate time to event analyses. Few studies used life table or hazard model approaches to reporting outcomes.

Direct Comparisons of Treatment Options. Randomized trials with common endpoints that reflect the treatment goals of women with fibroids must become a priority. Promising efficacy studies should be rapidly followed by larger effectiveness and comparison studies. Although changing entrenched treatment patterns is often difficult, especially for surgical procedures that have been clinically available in varied forms for decades, trials must be done that compare surgery to medication and to procedures. When possible, such as for women without or with mild symptoms, trials should include a delayed treatment arm or expectant management group in order to better understand the natural history of fibroids and to examine the degree to which symptoms may wax and wane.

Content Priorities. With the goal of achieving care tailored to the individual woman's fibroid status and characteristics, we need sophisticated information about a considerable array of issues. These include the burden of disease for both her and, possibly, her family; along with societal costs from loss of ability to function well in the usual family or occupational roles. Transitions associated with appearance of uterine fibroids, growth patterns, and influences on growth (e.g., concurrent medical conditions like diabetes, use of medications like hormonal contraception, influence of lactation and duration) are also high-priority topics, as are predictors of symptom development and resolution. Variation in care-seeking behaviors, differences in severity at presentation, and health and quality-of-life outcomes with and without treatment are yet other matters that investigators should attempt to address. Indeed this literature cannot currently address from trials whether disparities between white and black women in the age at appearance of fibroids and in the number and size of fibroids also foreshadows different treatment outcomes and durability of results.

Current practice suggests that women without symptoms may forego intervention because of the general belief that care should be aimed at improving symptoms or addressing a specific clinical concern such as difficulty conceiving or recurrent pregnancy loss. Although foregoing intervention can be wise in the absence of data that the intervention will prevent future difficulties, nonetheless we emphasize that no data yet support expectant management as a "safe" choice; neither do any data indicate whether use of therapeutics short of surgery might forestall or prevent future changes in fibroids or appearance of symptoms. The concept of preventive strategies is appealing. However, as long as the etiology of fibroids remains unclear, medical treatment choices are few, and preliminary trials are not assessing lifestyle interventions, the prospect for dietary management, exercise, hormonal management, or other prevention trials is slim.

The clinical research agenda will likely depend on new translational research and large-scale epidemiology studies that are yet to be done. Much remains to be learned that will require large-

scale prospective observational studies of sufficient size and rigor to support time-to-event analysis of outcomes, such as that being conducted in the COMPARE Uterine Fibroids 10,000 woman cohort supported by AHRQ and PCORI. These studies may afford greater power to examine effect modification and to determine trajectories of care over a reproductive lifespan for women with fibroids.

While we did not review these topics, many of the trials raise the question of what underpins the presence of symptoms and what modifies risk of growth. We must also continue to invest in basic and translational research to understand the pathogenesis and pathophysiology of uterine fibroids. Such research is required to best guide selection of pathways for exploration of genetic determinants of the timing and severity of disease, gene-environment interactions that may influence onset and symptoms, proteomic and treatment targeting research, as well as to discover potential prevention strategies. Research effort must be focused on documenting first the course and consequences of uterine fibroids using optimal imaging strategies, then the modifiers of that course, so that we can offer women an accurate account of the likely outcome of expectant management based on their individual status.

Conclusions

In accord with the prior AHRQ systematic evidence review on management of uterine fibroids, we find a lack of high-quality evidence in several areas. Specifically notable is the lack of well-conducted trials in U.S. populations. Fewer than a quarter of the trials were conducted in the United States. Direct comparisons among treatment options remain sparse. No studies have explicitly evaluated expectant management, which is a crucial missing piece of the evidence about the natural history of disease that would provide information about whether symptoms relapse and remit even after a woman presents seeking resolution of symptoms. The literature must come to include uniformly longer followup to determine whether women's objectives for treatment were met by the intervention received. Few women have only one concern driving their desire for intervention, yet remarkably many trials are directed at evaluating a single outcome.

The range of options for medical management is expanding while no new agent has appeared that overcomes limitations of existing options such as hormonal side effects and restriction to short duration of treatment. Appearance of new fibroids and growth of existing fibroids is poorly studied among the management options that leave the uterus in situ. Data to help women with fibroids who desire a pregnancy make treatment decisions are problematic because they originate primarily in populations dominated by participants with known fertility impairments or adverse pregnancy outcomes and often the proportion of women who wished to conceive is not known.

Across management options, we must note that lack of evidence is not equivalent to evidence of no benefit or of harm. Some of these interventions are effective in some patients but ability to estimate based on patient characteristics who would benefit most, or risk most, is lacking. Uncontrolled studies are not a substitute since they are notably biased for overestimating the degree of benefit subsequently reported in randomized trials. Indeed, not uncommonly, trials negate the findings of what in this case is largely retrospective and case series research. The current state of the literature does not permit definitive conclusions about comparative benefit, harm, or relative costs to achieve similar results across the range of available options and lacks strength of evidence for interventions such as use of continuous birth control pill regimens, progesterone containing IUDs, and endometrial ablation that are often used in routine clinical practice. Given how common and concerning fibroids can be to women and their care providers,

a redoubled emphasis on promoting high-quality fibroid research in the United States is imperative. Women deserve better information to guide their choices.

Abbreviations

AOR	adjusted odds ratio
aPVA	acrylamido polyvinyl alcohol
AUB	abnormal uterine bleeding
BISF-W	Brief Index of Sexual Functioning for Women
BMD	body mineral density
BMI	body mass index
cc	cubic centimeter
CEUS	contrasted enhanced ultrasound
CI	confidence interval
cm	centimeter
cm/s	centimeters per second
cm^3	cubic centimeters
CrI	credible interval
E2	estradiol
EBL	estimated blood loss
EQ-5D™	EuroQol Group standardized quality of life instrument, EQ-5D
FSH	follicle-stimulating hormone
g	gram
g/dl	grams per deciliter
GnRH	gonadotropin releasing hormone
GnRHa	gonadotropin releasing hormone agonist/analogue
GSP	gelatin sponge particles
GSP	gelatin sponge particle
HRQoL	health-related quality of life
Hct	hematocrit
Hgb	Hemoglobin
hrs	hours
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IQR	interquartile range
IEI	intratumoral ethanol injection
IM	Intramuscular
IU	international units
IU/L	international units per liter
kg	kilograms
LA-MLT	laparoscopically assisted minilaparotomy
LAVH	laparoscopically assisted vaginal hysterectomy
lb	pound
LBC	laparoscopic bipolar coagulation
LSA	laparoscopic supracervical amputation
LUAO	laparoscopic uterine artery occlusion
LUNA	laparoscopic uterine nerve ablation
mg	milligram
mg/d	milligrams per day
mg/dL	milligram per deciliter
min	minute(s)

ml	milliliter
MLT	minilaparotomy
mlU/mL	milli-international units per million
mm	millimeter
mmol/L	millimoles per liter
mos	months
MPA	Medroxyprogesterone Acetate
MR	magnetic resonance
MRgFUS	magnetic resonance guided focused ultrasound
MRI	magnetic resonance imaging
N	number
NA	not applicable
ng/ml	nanogram/milliliter
nmol/l	nanomoles per liter
nPVA	non-spherical polyvinyl alcohol
NR	not reported
NS	not significant
NSAIDs	non-steroidal anti-inflammatory drugs
OCP	oral contraceptive pill
OR	odds ratio
pmol/L	picomoles per liter
PVA	polyvinyl alcohol microspheres
RCT	randomized controlled trial
RR	relative risk
SAQ	Sexual Activity Questionnaire
SD	standard deviation
SEM	standard error of mean
SPVA	spherical polyvinyl alcohol
SSS	symptom severity scale
TAGM	tris-acryl gel microspheres
TAH	total abdominal hysterectomy
TCRE	transcervical resection of endometrium
TCRM	transcervical resection of submucous fibroids
UAE	uterine artery embolization
UAO	uterine artery occlusion
UFS-QOL	Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire
UK	United Kingdom
US	United States
VAS	Visual Analog Scale
vs.	versus

References

References

1. Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003 Jan;188(1):100-7 PMID: 12548202

2. Wise LA, Palmer JR, Stewart EA, et al. Age-specific incidence rates for self-reported uterine leiomyomata in the Black Women's Health Study. Obstet Gynecol. 2005 Mar;105(3):563-8. doi: 10.1097/01.AOG.0000154161.03418.e3 PMID: 15738025

3. Laughlin SK, Baird DD, Savitz DA, et al. Prevalence of uterine leiomyomas in the first trimester of pregnancy: an ultrasound-screening study. Obstet Gynecol. 2009 Mar;113(3):630-5. doi: 10.1097/AOG.0b013e318197bbaf PMID: 19300327

4. Monte LM ER. Fertility of Women in the United States: June 2012. Current Population Reports. 2014:P20-575

5. Myers ER, Barber MD, Gustilo-Ashby T, et al. Management of uterine leiomyomata: what do we really know? Obstet Gynecol. 2002 Jul;100(1):8-17 PMID: 12100798

6. Wegienka G, Baird DD, Hertz-Picciotto I, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003 Mar;101(3):431-7 PMID: 12636944

7. Stewart EA. Uterine fibroids. Lancet. 2001 Jan 27;357(9252):293-8. doi: 10.1016/s0140-6736(00)03622-9 PMID: 11214143

8. Huyck KL, Panhuysen CI, Cuenco KT, et al. The impact of race as a risk factor for symptom severity and age at diagnosis of uterine leiomyomata among affected sisters. Am J Obstet Gynecol. 2008 Feb;198(2):168 e1-9. doi: 10.1016/j.ajog.2007.05.038 PMID: 18226615

9. Segars JH, Parrott EC, Nagel JD, et al. Proceedings from the Third National Institutes of Health International Congress on Advances in Uterine Leiomyoma Research: comprehensive review, conference summary and future recommendations. Hum Reprod Update. 2014 May-Jun;20(3):309-33. doi: 10.1093/humupd/dmt058 PMID: 24401287

10. Hartmann KE, Birnbaum H, Ben-Hamadi R, et al. Annual costs associated with diagnosis of uterine leiomyomata. Obstet Gynecol. 2006 Oct;108(4):930-7. doi: 10.1097/01.aog.0000234651.41000.58 PMID: 17012456

11. Cardozo ER, Clark AD, Banks NK, et al. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012 Mar;206(3):211.e1-9. doi: 10.1016/j.ajog.2011.12.002 PMID: 22244472

12. Wechter ME, Stewart EA, Myers ER, et al. Leiomyoma-related hospitalization and surgery: prevalence and predicted growth based on population trends. Am J Obstet Gynecol. 2011 Nov;205(5):492 e1-5. doi: 10.1016/j.ajog.2011.07.008 PMID: 22035951

13. Whiteman MK, Hillis SD, Jamieson DJ, et al. Inpatient hysterectomy surveillance in the United States, 2000-2004. Am J Obstet Gynecol. 2008 Jan;198(1):34 e1-7. doi: 10.1016/j.ajog.2007.05.039 PMID: 17981254

14. Gliklich R, Leavy M, Velentgas P, et al. Identification of Future Research Needs in the Comparative Management of Uterine Fibroid Disease. AHRQ Publication No. 11-EHC023-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2011.

15. Zimmermann A, Bernuit D, Gerlinger C, et al. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Womens Health. 2012;12:6. doi: 10.1186/1472-6874-12-6 PMID: 22448610

16. Center for Devices and Radiological Health. Laparoscopic Uterine Power Morcellation in Hysterectomy and Myomectomy: FDA Safety Communication, Updated [WebContent]. US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm424443.htm.

17. Viswanathan M, Hartmann K, McKoy N, et al. Management of uterine fibroids: an update of the evidence. Evid Rep Technol Assess (Full Rep). 2007 Jul(154):1-122 PMID: 18288885

18. Pritts EA, Vanness DJ, Berek JS, et al. The prevalence of occult leiomyosarcoma at surgery for presumed uterine fibroids: a meta-analysis. Gynecol Surg. 2015;12(3):165-77. doi: 10.1007/s10397-015-0894-4 PMID: 26283890

19. Spies JB, Warren EH, Mathias SD, et al. Uterine fibroid embolization: measurement of health-related quality of life before and after therapy. J Vasc Interv Radiol. 1999 Nov-Dec;10(10):1293-303 PMID: 10584643

20. Coyne KS, Margolis MK, Murphy J, et al. Validation of the UFS-QOL-hysterectomy questionnaire: modifying an existing measure for comparative effectiveness research. Value Health. 2012 Jul-Aug;15(5):674-9. doi: 10.1016/j.jval.2012.03.1387 PMID: 22867776

21. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 12-EHC047-EF. Rockville MD: Agency for Healthcare Research and Quality; March 2012. www.effectivehealthcare.ahrq.gov/

22. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions for the effective health care program of the Agency for Healthcare Research and Quality: An update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 13(14)-EHC 130-EF. Rockville, MD: Agency for Healthcare Research and Quality; November 2013. www.effectivehealthcare.ahrq.gov

23. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23. doi: 10.1016/j.jclinepi.2009.03.009 PMID: 19595577

24. Berkman ND, Lohr KN, Ansari M, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research

and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD); 2008.

25. Orsi F, Monfardini L, Bonomo G, et al. Ultrasound guided high intensity focused ultrasound (USgHIFU) ablation for uterine fibroids: Do we need the microbubbles? Int J Hyperthermia. 2015 Mar 11:1-7. doi: 10.3109/02656736.2015.1004134 PMID: 25758436

26. Donnez J, Hudecek R, Donnez O, et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertil Steril. 2015 Feb;103(2):519-27.e3. doi: 10.1016/j.fertnstert.2014.10.038 PMID: 25542821

27. Shlansky-Goldberg RD, Rosen MA, Mondschein JI, et al. Comparison of polyvinyl alcohol microspheres and tris-acryl gelatin microspheres for uterine fibroid embolization: results of a single-center randomized study. J Vasc Interv Radiol. 2014 Jun;25(6):823-32. doi: 10.1016/j.jvir.2014.03.009 PMID: 24788209

28. Sesti F, Cosi V, Calonzi F, et al. Randomized comparison of total laparoscopic, laparoscopically assisted vaginal and vaginal hysterectomies for myomatous uteri. Arch Gynecol Obstet. 2014 Sep;290(3):485-91. doi: 10.1007/s00404-014-3228-2 PMID: 24710800

29. Brucker SY, Hahn M, Kraemer D, et al. Laparoscopic radiofrequency volumetric thermal ablation of fibroids versus laparoscopic myomectomy. Int J Gynaecol Obstet. 2014 Jun;125(3):261-5. doi: 10.1016/j.ijgo.2013.11.012 PMID: 24698202

30. Yang Z, Zhang Y, Zhang R, et al. A case-control study of high-intensity focused ultrasound combined with sonographically guided intratumoral ethanol injection in the treatment of uterine fibroids. J Ultrasound Med. 2014 Apr;33(4):657-65. doi: 10.7863/ultra.33.4.657 PMID: 24658945

31. Donnez J, Vazquez F, Tomaszewski J, et al. Long-term treatment of uterine fibroids with ulipristal acetate. Fertil Steril. 2014 Jun;101(6):1565-73.e1-18. doi: 10.1016/j.fertnstert.2014.02.008 PMID: 24630081

32. Jiang N, Xie B, Zhang X, et al. Enhancing ablation effects of a microbubble-enhancing contrast agent ("SonoVue") in the treatment of uterine fibroids with high-intensity focused ultrasound: a randomized controlled trial. Cardiovasc Intervent Radiol. 2014 Oct;37(5):1321-8. doi: 10.1007/s00270-013-0803-z PMID: 24549267

33. Song YG, Jang H, Park KD, et al. Non spherical polyvinyl alcohol versus gelatin sponge particles for uterine artery embolization for symptomatic fibroids. Minim Invasive Ther Allied Technol. 2013 Dec;22(6):364-71. doi: 10.3109/13645706.2013.826674 PMID: 23992381

34. Ardovino M, Ardovino I, Castaldi MA, et al. Minilaparoscopic myomectomy: a mini-invasive technical variant. J Laparoendosc Adv Surg Tech A. 2013 Oct;23(10):871-5. doi: 10.1089/lap.2013.0037 PMID: 23992206

35. Carbonell JL, Acosta R, Perez Y, et al. Treatment of Uterine Myoma with 2.5 or 5 mg Mifepristone Daily during 3 Months with 9 Months Posttreatment Followup: Randomized Clinical Trial. ISRN Obstet Gynecol. 2013;2013:649030. doi: 10.1155/2013/649030 PMID: 23984082

36. Esteve JL, Acosta R, Perez Y, et al. Mifepristone versus placebo to treat uterine myoma: a double-blind, randomized clinical trial. Int J Womens Health. 2013;5:361-9. doi: 10.2147/ijwh.s42770 PMID: 23843709

37. Carbonell JL, Acosta R, Perez Y, et al. Safety and effectiveness of different dosage of mifepristone for the treatment of uterine fibroids: a double-blind randomized clinical trial. Int J Womens Health. 2013;5:115-24. doi: 10.2147/ijwh.s33125 PMID: 23658500

38. Eder S, Baker J, Gersten J, et al. Efficacy and safety of oral tranexamic acid in women with heavy menstrual bleeding and fibroids. Womens Health (Lond Engl). 2013 Jul;9(4):397-403. doi: 10.2217/whe.13.28 PMID: 23656203

39. Wang X, Qin J, Wang L, et al. Effect of high-intensity focused ultrasound on sexual function in the treatment of uterine fibroids: comparison to conventional myomectomy. Arch Gynecol Obstet. 2013 Oct;288(4):851-8. doi: 10.1007/s00404-013-2775-2 PMID: 23564052

40. Vercellino G, Erdemoglu E, Joe A, et al. Laparoscopic temporary clipping of uterine artery during laparoscopic myomectomy. Arch Gynecol Obstet. 2012 Nov;286(5):1181-6. doi: 10.1007/s00404-012-2419-y PMID: 22714065

41. Esteve JL, Acosta R, Perez Y, et al. Treatment of uterine myoma with 5 or 10mg mifepristone daily during 6 months, post-treatment evolution over 12 months: double-blind randomised clinical trial. Eur J Obstet Gynecol Reprod Biol. 2012 Apr;161(2):202-8. doi: 10.1016/j.ejogrb.2011.12.018 PMID: 22269473

42. Jun F, Yamin L, Xinli X, et al. Uterine artery embolization versus surgery for symptomatic uterine fibroids: a randomized controlled trial and a meta-analysis of the literature. Arch Gynecol Obstet. 2012 May;285(5):1407-13. doi: 10.1007/s00404-011-2065-9 PMID: 22048783

43. Yu SC, Lok I, Ho SS, et al. Comparison of clinical outcomes of tris-acryl microspheres versus polyvinyl alcohol microspheres for uterine artery embolization for leiomyomas: results of a randomized trial. J Vasc Interv Radiol. 2011 Sep;22(9):1229-35. doi: 10.1016/j.jvir.2011.05.011 PMID: 21802314

44. Manyonda IT, Bratby M, Horst JS, et al. Uterine artery embolization versus myomectomy: impact on quality of life--results of the FUME (Fibroids of the Uterus: Myomectomy versus Embolization) Trial. Cardiovasc Intervent Radiol. 2012 Jun;35(3):530-6. doi: 10.1007/s00270-011-0228-5 PMID: 21773858

45. Wang JJ, Yang F, Gao T, et al. Gasless laparoscopy versus conventional laparoscopy in uterine myomectomy: a single-centre randomized trial. J Int Med Res. 2011;39(1):172-8 PMID: 21672319

46. Liu M, Cheng Z, Zhu Y, et al. Prospective comparison of laparoscopic uterine artery occlusion plus myomectomy with classic intrafascial supracervical hysterectomy for symptomatic fibroid treatment: differences in post-operative quality-of-life measures. Eur J Obstet Gynecol Reprod Biol. 2011 Mar;155(1):79-84. doi: 10.1016/j.ejogrb.2010.10.022 PMID: 21216518

47. Worthington-Kirsch RL, Siskin GP, Hegener P, et al. Comparison of the efficacy of the embolic agents acrylamido polyvinyl alcohol microspheres and tris-acryl gelatin microspheres for uterine artery embolization for leiomyomas: a prospective randomized controlled trial. Cardiovasc Intervent Radiol. 2011 Jun;34(3):493-501. doi: 10.1007/s00270-010-0049-y PMID: 21127866

48. Bilhim T, Pisco JM, Duarte M, et al. Polyvinyl alcohol particle size for uterine artery embolization: a prospective randomized study of initial use of 350-500 mum particles versus initial use of 500-700 mum particles. J Vasc Interv Radiol. 2011 Jan;22(1):21-7. doi: 10.1016/j.jvir.2010.09.018 PMID: 21106390

49. Nieman LK, Blocker W, Nansel T, et al. Efficacy and tolerability of CDB-2914 treatment for symptomatic uterine fibroids: a randomized, double-blind, placebo-controlled, phase IIb study. Fertil Steril. 2011 Feb;95(2):767-72.e1-2. doi: 10.1016/j.fertnstert.2010.09.059 PMID: 21055739

50. Zhao F, Jiao Y, Guo Z, et al. Evaluation of loop ligation of larger myoma pseudocapsule combined with vasopressin on laparoscopic myomectomy. Fertil Steril. 2011 Feb;95(2):762-6. doi: 10.1016/j.fertnstert.2010.08.059 PMID: 20883988

51. Meng X, He G, Zhang J, et al. A comparative study of fibroid ablation rates using radio frequency or high-intensity focused ultrasound. Cardiovasc Intervent Radiol. 2010 Aug;33(4):794-9. doi: 10.1007/s00270-010-9909-8 PMID: 20544227

52. Ruuskanen A, Hippelainen M, Sipola P, et al. Uterine artery embolisation versus hysterectomy for leiomyomas: primary and 2-year follow-up results of a randomised prospective clinical trial. Eur Radiol. 2010 Oct;20(10):2524-32. doi: 10.1007/s00330-010-1829-0 PMID: 20526776

53. Sayyah-Melli M, Tehrani-Gadim S, Dastranj-Tabrizi A, et al. Comparison of the effect of gonadotropin-releasing hormone agonist and dopamine receptor agonist on uterine myoma growth. Histologic, sonographic, and intra-operative changes. Saudi Med J. 2009 Aug;30(8):1024-33 PMID: 19668882

54. Cicinelli E, Tinelli R, Colafiglio G, et al. Laparoscopy vs minilaparotomy in women with symptomatic uterine myomas: a prospective randomized study. J Minim Invasive Gynecol. 2009 Jul-Aug;16(4):422-6. doi: 10.1016/j.jmig.2009.03.011 PMID: 19573818

55. Tan J, Sun Y, Zhong B, et al. A randomized, controlled study comparing minilaparotomy versus isobaric gasless laparoscopic assisted minilaparotomy myomectomy for removal of large uterine myomas: short-term outcomes. Eur J Obstet Gynecol Reprod Biol. 2009 Jul;145(1):104-8. doi: 10.1016/j.ejogrb.2009.04.015 PMID: 19427094

56. Parsanezhad ME, Azmoon M, Alborzi S, et al. A randomized, controlled clinical trial comparing the effects of aromatase inhibitor (letrozole) and gonadotropin-releasing hormone agonist (triptorelin) on uterine leiomyoma volume and hormonal status. Fertil Steril. 2010 Jan;93(1):192-8. doi: 10.1016/j.fertnstert.2008.09.064 PMID: 19135657

57. Carbonell Esteve JL, Acosta R, Heredia B, et al. Mifepristone for the treatment of uterine leiomyomas: a randomized controlled trial. Obstet Gynecol. 2008 Nov;112(5):1029-36. doi: 10.1097/AOG.0b013e31818aa930 PMID: 18978102

58. Sesti F, Ruggeri V, Pietropolli A, et al. Laparoscopically assisted vaginal hysterectomy versus vaginal hysterectomy for enlarged uterus. Jsls. 2008 Jul-Sep;12(3):246-51 PMID: 18765046

59. Tan J, Sun Y, Dai H, et al. A randomized trial of laparoscopic versus laparoscopic-assisted minilaparotomy myomectomy for removal of large uterine myoma: short-term outcomes. J Minim Invasive Gynecol. 2008 Jul-Aug;15(4):402-9. doi: 10.1016/j.jmig.2008.03.010 PMID: 18602045

60. Levens ED, Potlog-Nahari C, Armstrong AY, et al. CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial. Obstet Gynecol. 2008 May;111(5):1129-36. doi: 10.1097/AOG.0b013e3181705d0e PMID: 18448745

61. Cunningham E, Barreda L, Ngo M, et al. Uterine artery embolization versus occlusion for uterine leiomyomas: a pilot randomized clinical trial. J Minim Invasive Gynecol. 2008 May-Jun;15(3):301-7. doi: 10.1016/j.jmig.2008.01.011 PMID: 18439501

62. Siskin GP, Beck A, Schuster M, et al. Leiomyoma infarction after uterine artery embolization: a prospective randomized study comparing tris-acryl gelatin microspheres versus polyvinyl alcohol microspheres. J Vasc Interv Radiol. 2008 Jan;19(1):58-65. doi: 10.1016/j.jvir.2007.08.034 PMID: 18192468

63. Palomba S, Orio F, Jr., Falbo A, et al. Tibolone reverses the cognitive effects caused by leuprolide acetate administration, improving mood and quality of life in patients with symptomatic uterine leiomyomas. Fertil Steril. 2008 Jul;90(1):165-73. doi: 10.1016/j.fertnstert.2007.05.061 PMID: 18001721

64. Sesti F, Capobianco F, Capozzolo T, et al. Isobaric gasless laparoscopy versus minilaparotomy in uterine myomectomy: a randomized trial. Surg Endosc. 2008 Apr;22(4):917-23. doi: 10.1007/s00464-007-9516-1 PMID: 17705083

65. Morris EP, Rymer J, Robinson J, et al. Efficacy of tibolone as "add-back therapy" in conjunction with a gonadotropin-releasing hormone analogue in the treatment of uterine fibroids. Fertil Steril. 2008 Feb;89(2):421-8. doi: 10.1016/j.fertnstert.2007.02.064 PMID: 17572410

66. Palomba S, Zupi E, Falbo A, et al. A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: reproductive outcomes. Fertil Steril. 2007 Oct;88(4):933-41. doi: 10.1016/j.fertnstert.2006.12.047 PMID: 17434505

67. Melli MS, Farzadi L, Madarek EO. Comparison of the effect of gonadotropin-releasing hormone analog (Diphereline) and Cabergoline (Dostinex) treatment on uterine myoma regression. Saudi Med J. 2007 Mar;28(3):445-50 PMID: 17334477

68. Chwalisz K, Larsen L, Mattia-Goldberg C, et al. A randomized, controlled trial of asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata. Fertil Steril. 2007 Jun;87(6):1399-412. doi: 10.1016/j.fertnstert.2006.11.094 PMID: 17307170

69. Edwards RD, Moss JG, Lumsden MA, et al. Uterine-artery embolization versus surgery for symptomatic uterine fibroids. N Engl J Med. 2007 Jan 25;356(4):360-70. doi: 10.1056/NEJMoa062003 PMID: 17251532

70. Hald K, Klow NE, Qvigstad E, et al. Laparoscopic occlusion compared with embolization of uterine vessels: a randomized controlled trial. Obstet Gynecol. 2007 Jan;109(1):20-7. doi: 10.1097/01.aog.0000249602.39339.31 PMID: 17197583

71. Fiscella K, Eisinger SH, Meldrum S, et al. Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. Obstet Gynecol. 2006 Dec;108(6):1381-7. doi: 10.1097/01.AOG.0000243776.23391.7b PMID: 17138770

72. Casini ML, Rossi F, Agostini R, et al. Effects of the position of fibroids on fertility. Gynecol Endocrinol. 2006 Feb;22(2):106-9. doi: 10.1080/09513590600604673 PMID: 16603437

73. Vilos GA, Vilos AG, Abu-Rafea B, et al. Administration of goserelin acetate after uterine artery embolization does not change the reduction rate and volume of uterine myomas. Fertil Steril. 2006 May;85(5):1478-83. doi: 10.1016/j.fertnstert.2005.10.039 PMID: 16579996

74. Alessandri F, Lijoi D, Mistrangelo E, et al. Randomized study of laparoscopic versus minilaparotomic myomectomy for uterine myomas. J Minim Invasive Gynecol. 2006 Mar-Apr;13(2):92-7. doi: 10.1016/j.jmig.2005.11.008 PMID: 16527709

75. Silva-Filho AL, Werneck RA, de Magalhaes RS, et al. Abdominal vs vaginal hysterectomy: a comparative study of the postoperative quality of life and satisfaction. Arch Gynecol Obstet. 2006 Apr;274(1):21-4. doi: 10.1007/s00404-005-0118-7 PMID: 16408185

76. Spies JB, Allison S, Flick P, et al. Spherical polyvinyl alcohol versus tris-acryl gelatin microspheres for uterine artery embolization for leiomyomas: results of a limited randomized comparative study. J Vasc Interv Radiol. 2005 Nov;16(11):1431-7. doi: 10.1097/01.rvi.0000179793.69590.1a PMID: 16319148

77. Mara M, Fucikova Z, Maskova J, et al. Uterine fibroid embolization versus myomectomy in women wishing to preserve fertility: preliminary results of a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2006 Jun 1;126(2):226-33. doi: 10.1016/j.ejogrb.2005.10.008 PMID: 16293363

78. Hehenkamp WJ, Volkers NA, Donderwinkel PF, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids (EMMY trial): peri- and postprocedural results from a randomized controlled trial. Am J Obstet Gynecol. 2005 Nov;193(5):1618-29. doi: 10.1016/j.ajog.2005.05.017 PMID: 16260201

79. Spies JB, Allison S, Flick P, et al. Polyvinyl alcohol particles and tris-acryl gelatin microspheres for uterine artery embolization for leiomyomas: results of a randomized comparative study. J Vasc Interv Radiol. 2004 Aug;15(8):793-800. doi: 10.1097/01.rvi.0000136982.42548.5d PMID: 15297582

80. Jirecek S, Lee A, Pavo I, et al. Raloxifene prevents the growth of uterine leiomyomas in premenopausal women. Fertil Steril. 2004 Jan;81(1):132-6 PMID: 14711556

81. Eisinger SH, Meldrum S, Fiscella K, et al. Low-dose mifepristone for uterine leiomyomata. Obstet Gynecol. 2003 Feb;101(2):243-50 PMID: 12576246

82. Pinto I, Chimeno P, Romo A, et al. Uterine fibroids: uterine artery embolization versus abdominal hysterectomy for treatment--a prospective, randomized, and controlled clinical trial. Radiology. 2003 Feb;226(2):425-31. doi: 10.1148/radiol.2262011716 PMID: 12563136

83. Hwang JL, Seow KM, Tsai YL, et al. Comparative study of vaginal, laparoscopically assisted vaginal and abdominal hysterectomies for uterine myoma larger than 6 cm in diameter or uterus weighing at least 450 g: a prospective randomized study. Acta Obstet Gynecol Scand. 2002 Dec;81(12):1132-8 PMID: 12519109

84. Benassi L, Rossi T, Kaihura CT, et al. Abdominal or vaginal hysterectomy for enlarged uteri: a randomized clinical trial. Am J Obstet Gynecol. 2002 Dec;187(6):1561-5 PMID: 12501064

85. Palomba S, Russo T, Orio F, Jr., et al. Effectiveness of combined GnRH analogue plus raloxifene administration in the treatment of uterine leiomyomas: a prospective, randomized, single-blind, placebo-controlled clinical trial. Hum Reprod. 2002 Dec;17(12):3213-9 PMID: 12456626

86. Palomba S, Orio F, Jr., Morelli M, et al. Raloxifene administration in premenopausal women with uterine leiomyomas: a pilot study. J Clin Endocrinol Metab. 2002 Aug;87(8):3603-8. doi: 10.1210/jcem.87.8.8747 PMID: 12161482

87. Simsek T, Karakus C, Trak B. Impact of different hormone replacement therapy regimens on the size of myoma uteri in postmenopausal period: tibolone versus transdermal hormonal replacement system. Maturitas. 2002 Jul 25;42(3):243-6 PMID: 12161049

88. Seracchioli R, Venturoli S, Vianello F, et al. Total laparoscopic hysterectomy compared with abdominal hysterectomy in the presence of a large uterus. J Am Assoc Gynecol Laparosc. 2002 Aug;9(3):333-8 PMID: 12101331

89. Yen YK, Liu WM, Yuan CC, et al. Comparison of two procedures for laparoscopic-assisted vaginal hysterectomy of large myomatous uteri. J Am Assoc Gynecol Laparosc. 2002 Feb;9(1):63-9 PMID: 11821608

90. Yen YK, Liu WM, Yuan CC, et al. Addition of laparoscopic uterine nerve ablation to laparoscopic bipolar coagulation of uterine vessels for women with uterine myomas and dysmenorrhea. J Am Assoc Gynecol Laparosc. 2001 Nov;8(4):573-8 PMID: 11677339

91. Palomba S, Sammartino A, Di Carlo C, et al. Effects of raloxifene treatment on uterine leiomyomas in postmenopausal women. Fertil Steril. 2001 Jul;76(1):38-43 PMID: 11438317

92. Sadan O, Ginath S, Sofer D, et al. The role of tamoxifen in the treatment of symptomatic uterine leiomyomata -- a pilot study. Eur J Obstet Gynecol Reprod Biol. 2001 Jun;96(2):183-6 PMID: 11384804

93. Rossetti A, Sizzi O, Soranna L, et al. Long-term results of laparoscopic myomectomy: recurrence rate in comparison with abdominal myomectomy. Hum Reprod. 2001 Apr;16(4):770-4 PMID: 11278231

94. Soriano D, Goldstein A, Lecuru F, et al. Recovery from vaginal hysterectomy compared with laparoscopy-assisted vaginal hysterectomy: a prospective, randomized, multicenter study. Acta Obstet Gynecol Scand. 2001 Apr;80(4):337-41 PMID: 11264609

95. Soysal ME, Soysal SK, Vicdan K. Thermal balloon ablation in myoma-induced menorrhagia under local anesthesia. Gynecol Obstet Invest. 2001;51(2):128-33. doi: 52908 PMID: 11223708

96. Takeuchi H, Kobori H, Kikuchi I, et al. A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis. J Obstet Gynaecol Res. 2000 Oct;26(5):325-31 PMID: 11147718

97. Seracchioli R, Rossi S, Govoni F, et al. Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. Hum Reprod. 2000 Dec;15(12):2663-8 PMID: 11098042

98. Ferrari MM, Berlanda N, Mezzopane R, et al. Identifying the indications for laparoscopically assisted vaginal hysterectomy: a prospective, randomised comparison with abdominal hysterectomy in patients with symptomatic uterine fibroids. Bjog. 2000 May;107(5):620-5 PMID: 10826576

99. Fedele L, Bianchi S, Raffaelli R, et al. A randomized study of the effects of tibolone and transdermal estrogen replacement therapy in postmenopausal women with uterine myomas. Eur J Obstet Gynecol Reprod Biol. 2000 Jan;88(1):91-4 PMID: 10659924

100. Parazzini F, Bortolotti A, Chiantera V, et al. Goserelin acetate to avoid hysterectomy in pre-menopausal women with fibroids requiring surgery. Eur J Obstet Gynecol Reprod Biol. 1999 Nov;87(1):31-3 PMID: 10579613

101. Palomba S, Affinito P, Tommaselli GA, et al. A clinical trial of the effects of tibolone administered with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata. Fertil Steril. 1998 Jul;70(1):111-8 PMID: 9660431

102. Gregoriou O, Vitoratos N, Papadias C, et al. Effect of tibolone on postmenopausal women with myomas. Maturitas. 1997 Jun;27(2):187-91 PMID: 9255754

103. Broekmans FJ, Hompes PG, Heitbrink MA, et al. Two-step gonadotropin-releasing hormone agonist treatment of uterine leiomyomas: standard-dose therapy followed by reduced-dose therapy. Am J Obstet Gynecol. 1996 Nov;175(5):1208-16 PMID: 8942490

104. Mais V, Ajossa S, Guerriero S, et al. Laparoscopic versus abdominal myomectomy: a prospective, randomized trial to evaluate benefits in early outcome. Am J Obstet Gynecol. 1996 Feb;174(2):654-8 PMID: 8623802

105. Scialli AR, Jestila KJ. Sustained benefits of leuprolide acetate with or without subsequent medroxyprogesterone acetate in the nonsurgical management of leiomyomata uteri. Fertil Steril. 1995 Aug;64(2):313-20 PMID: 7615109

106. Friedman AJ, Daly M, Juneau-Norcross M, et al. A prospective, randomized trial of gonadotropin-releasing hormone agonist plus estrogen-progestin or progestin "add-back" regimens for women with leiomyomata uteri. J Clin Endocrinol Metab. 1993 Jun;76(6):1439-45. doi: 10.1210/jcem.76.6.8501148 PMID: 8501148

107. Carr BR, Marshburn PB, Weatherall PT, et al. An evaluation of the effect of gonadotropin-releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double blind, placebo-controlled, crossover trial. J Clin Endocrinol Metab. 1993 May;76(5):1217-23. doi: 10.1210/jcem.76.5.8496313 PMID: 8496313

108. Watanabe Y, Nakamura G, Matsuguchi H, et al. Efficacy of a low-dose leuprolide acetate depot in the treatment of uterine leiomyomata in Japanese women. Fertil Steril. 1992 Jul;58(1):66-71 PMID: 1624025

109. Friedman AJ, Hoffman DI, Comite F, et al. Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. The Leuprolide Study Group. Obstet Gynecol. 1991 May;77(5):720-5 PMID: 1901638

110. Fedele L, Bianchi S, Baglioni A, et al. Intranasal buserelin versus surgery in the treatment of uterine leiomyomata: long-term follow-up. Eur J Obstet Gynecol Reprod Biol. 1991 Jan 4;38(1):53-7 PMID: 1899079

111. Costantini S, Anserini P, Valenzano M, et al. Luteinizing hormone-releasing hormone analog therapy of uterine fibroid: analysis of results obtained with buserelin administered intranasally and goserelin

administered subcutaneously as a monthly depot. Eur J Obstet Gynecol Reprod Biol. 1990 Oct;37(1):63-9 PMID: 2142921

112. Friedman AJ, Harrison-Atlas D, Barbieri RL, et al. A randomized, placebo-controlled, double-blind study evaluating the efficacy of leuprolide acetate depot in the treatment of uterine leiomyomata. Fertil Steril. 1989 Feb;51(2):251-6 PMID: 2492232

113. Friedman AJ, Barbieri RL, Doubilet PM, et al. A randomized, double-blind trial of a gonadotropin releasing-hormone agonist (leuprolide) with or without medroxyprogesterone acetate in the treatment of leiomyomata uteri. Fertil Steril. 1988 Mar;49(3):404-9 PMID: 2963759

114. Tosun AK, Tosun I, Suer N. Comparison of levonorgestrel-releasing intrauterine device with oral progestins in heavy menstrual bleeding (HMB) cases with uterine leiomyoma (LNG-IUD and oral progestin usage in myoma uteri). Pak J Med Sci. 2014 Jul;30(4):834-9 PMID: 25097527

115. Wang X, Qin J, Chen J, et al. The effect of high-intensity focused ultrasound treatment on immune function in patients with uterine fibroids. Int J Hyperthermia. 2013 May;29(3):225-33. doi: 10.3109/02656736.2013.775672 PMID: 23537008

116. van der Kooij SM, Hehenkamp WJ, Birnie E, et al. The effect of treatment preference and treatment allocation on patients' health-related quality of life in the randomized EMMY trial. Eur J Obstet Gynecol Reprod Biol. 2013 Jul;169(1):69-74. doi: 10.1016/j.ejogrb.2013.01.019 PMID: 23474384

117. Ananthakrishnan G, Murray L, Ritchie M, et al. Randomized comparison of uterine artery embolization (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): subanalysis of 5-year MRI findings. Cardiovasc Intervent Radiol. 2013 Jun;36(3):676-81. doi: 10.1007/s00270-012-0485-y PMID: 23070101

118. Moss JG, Cooper KG, Khaund A, et al. Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-year results. Bjog. 2011 Jul;118(8):936-44. doi: 10.1111/j.1471-0528.2011.02952.x PMID: 21481151

119. van der Kooij SM, Hehenkamp WJ, Volkers NA, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2010 Aug;203(2):105.e1-13. doi: 10.1016/j.ajog.2010.01.049 PMID: 20579960

120. Rashid S, Khaund A, Murray LS, et al. The effects of uterine artery embolisation and surgical treatment on ovarian function in women with uterine fibroids. Bjog. 2010 Jul;117(8):985-9. doi: 10.1111/j.1471-0528.2010.02579.x PMID: 20465558

121. Hald K, Noreng HJ, Istre O, et al. Uterine artery embolization versus laparoscopic occlusion of uterine arteries for leiomyomas: long-term results of a randomized comparative trial. J Vasc Interv Radiol. 2009 Oct;20(10):1303-10; quiz 11. doi: 10.1016/j.jvir.2009.07.022 PMID: 19713130

122. Volkers NA, Hehenkamp WJ, Smit P, et al. Economic evaluation of uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: results from the randomized EMMY trial. J Vasc Interv Radiol. 2008 Jul;19(7):1007-16; quiz 17. doi: 10.1016/j.jvir.2008.03.001 PMID: 18589314

123. Hehenkamp WJ, Volkers NA, Birnie E, et al. Symptomatic uterine fibroids: treatment with uterine artery embolization or hysterectomy--results from the randomized clinical Embolisation versus Hysterectomy (EMMY) Trial. Radiology. 2008 Mar;246(3):823-32. doi: 10.1148/radiol.2463070260 PMID: 18187401

124. Mara M, Maskova J, Fucikova Z, et al. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. Cardiovasc Intervent Radiol. 2008 Jan-Feb;31(1):73-85. doi: 10.1007/s00270-007-9195-2 PMID: 17943348

125. Hehenkamp WJ, Volkers NA, Bartholomeus W, et al. Sexuality and body image after uterine artery embolization and hysterectomy in the treatment of uterine fibroids: a randomized comparison. Cardiovasc Intervent Radiol. 2007 Sep-Oct;30(5):866-75. doi: 10.1007/s00270-007-9121-7 PMID: 17671809

126. Hehenkamp WJ, Volkers NA, Broekmans FJ, et al. Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy. Hum Reprod. 2007 Jul;22(7):1996-2005. doi: 10.1093/humrep/dem105 PMID: 17582145

127. Volkers NA, Hehenkamp WJ, Birnie E, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2007 Jun;196(6):519.e1-11. doi: 10.1016/j.ajog.2007.02.029 PMID: 17547877

128. Palomba S, Zupi E, Russo T, et al. A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: short-term outcomes. Fertil Steril. 2007 Oct;88(4):942-51. doi: 10.1016/j.fertnstert.2006.12.048 PMID: 17349643

129. Volkers NA, Hehenkamp WJ, Birnie E, et al. Uterine artery embolization in the treatment of symptomatic uterine fibroid tumors (EMMY trial): periprocedural results and complications. J Vasc Interv Radiol. 2006 Mar;17(3):471-80. doi: 10.1097/01.rvi.0000203419.61693.84 PMID: 16567671

130. Hehenkamp WJ, Volkers NA, Birnie E, et al. Pain and return to daily activities after uterine artery embolization and hysterectomy in the treatment of symptomatic uterine fibroids: results from the randomized EMMY trial. Cardiovasc Intervent Radiol. 2006 Mar-Apr;29(2):179-87. doi: 10.1007/s00270-005-0195-9 PMID: 16447002

131. Eisinger SH, Bonfiglio T, Fiscella K, et al. Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. J Minim Invasive Gynecol. 2005 May-Jun;12(3):227-33. doi: 10.1016/j.jmig.2005.01.022 PMID: 15922980

132. Palomba S, Orio F, Jr., Russo T, et al. Gonadotropin-releasing hormone agonist with or without raloxifene: effects on cognition, mood, and quality of life. Fertil Steril. 2004 Aug;82(2):480-2. doi: 10.1016/j.fertnstert.2003.11.061 PMID: 15302308

133. Friedman AJ, Daly M, Juneau-Norcross M, et al. Long-term medical therapy for leiomyomata uteri: a prospective, randomized study of leuprolide acetate depot plus either oestrogen-progestin or progestin 'add-back' for 2 years. Hum Reprod. 1994 Sep;9(9):1618-25 PMID: 7836510

134. Okin CR, Guido RS, Meyn LA, et al. Vasopressin during abdominal hysterectomy: a randomized controlled trial. Obstet Gynecol. 2001 Jun;97(6):867-72 PMID: 11384687

135. Lethaby A, Vollenhoven B, Sowter M. Efficacy of pre-operative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy: a systematic review. Bjog. 2002 Oct;109(10):1097-108 PMID: 12387461

136. Blithe DL, Nieman LK, Blye RP, et al. Development of the selective progesterone receptor modulator CDB-2914 for clinical indications. Steroids. 2003 Nov;68(10-13):1013-7 PMID: 14667994

137. Passaro MD, Piquion J, Mullen N, et al. Luteal phase dose-response relationships of the antiprogestin CDB-2914 in normally cycling women. Hum Reprod. 2003 Sep;18(9):1820-7 PMID: 12923133

138. Katzka DA, Smyrk TC, Chial HJ, et al. Esophageal leiomyomatosis presenting as achalasia diagnosed by high-resolution manometry and endoscopic core biopsy. Gastrointest Endosc. 2012 Jul;76(1):216-7. doi: 10.1016/j.gie.2011.07.076 PMID: 22305508

139. Friedl A, Jordan VC. What do we know and what don't we know about tamoxifen in the human uterus. Breast Cancer Res Treat. 1994;31(1):27-39 PMID: 7981454

140. Stewart EA, Rabinovici J, Tempany CM, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril. 2006 Jan;85(1):22-9. doi: 10.1016/j.fertnstert.2005.04.072 PMID: 16412721

141. Hindley J, Gedroyc WM, Regan L, et al. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. AJR Am J Roentgenol. 2004 Dec;183(6):1713-9. doi: 10.2214/ajr.183.6.01831713 PMID: 15547216

142. Berman JM, Guido RS, Garza Leal JG, et al. Three-year outcome of the Halt trial: a prospective analysis of radiofrequency volumetric thermal ablation of myomas. J Minim Invasive Gynecol. 2014 Sep-Oct;21(5):767-74. doi: 10.1016/j.jmig.2014.02.015 PMID: 24613404

143. Chudnoff SG, Berman JM, Levine DJ, et al. Outpatient procedure for the treatment and relief of symptomatic uterine myomas. Obstet Gynecol. 2013 May;121(5):1075-82. doi: 10.1097/AOG.0b013e31828b7962 PMID: 23635746

144. Guido RS, Macer JA, Abbott K, et al. Radiofrequency volumetric thermal ablation of fibroids: a prospective, clinical analysis of two years' outcome from the Halt trial. Health Qual Life Outcomes. 2013;11:139. doi: 10.1186/1477-7525-11-139 PMID: 23941588

145. Saienko VF, Miasoiedov SD, Andreieshchev SA, et al. [Diagnosis and treatment of esophageal leyomyoma]. Klin Khir. 2006 Oct(10):14-7 PMID: 17269399

146. Vilos GA, Allaire C, Laberge PY, et al. The management of uterine leiomyomas. J Obstet Gynaecol Can. 2015 Feb;37(2):157-81 PMID: 25767949

147. Learman LA, Summitt RL, Jr., Varner RE, et al. A randomized comparison of total or supracervical hysterectomy: surgical complications and clinical outcomes. Obstet Gynecol. 2003 Sep;102(3):453-62 PMID: 12962924

148. Zhang J, Li T, Zhang J, et al. Clinical Characteristics and Prognosis of Unexpected Uterine Sarcoma After Hysterectomy for Presumed Myoma With and Without Transvaginal Scalpel Morcellation. Int J Gynecol Cancer. 2016 Jan 20. doi: 10.1097/igc.0000000000000638 PMID: 26807642

149. Balgobin S, Maldonado PA, Chin K, et al. Safety Of Manual Morcellation Following Vaginal Or Laparoscopic-Assisted Vaginal Hysterectomy. J Minim Invasive Gynecol. 2016 Jan 20. doi: 10.1016/j.jmig.2016.01.014 PMID: 26802908

150. Rodriguez AM, Asoglu MR, Sak ME, et al. Incidence of occult leiomyosarcoma in presumed morcellation cases: a database study. Eur J Obstet Gynecol Reprod Biol. 2015 Nov 28;197:31-5. doi: 10.1016/j.ejogrb.2015.11.009 PMID: 26699101

151. Raine-Bennett T, Tucker LY, Zaritsky E, et al. Occult Uterine Sarcoma and Leiomyosarcoma: Incidence of and Survival Associated With Morcellation. Obstet Gynecol. 2016 Jan;127(1):29-39. doi: 10.1097/aog.0000000000001187 PMID: 26646120

152. Zhao WC, Bi FF, Li D, et al. Incidence and clinical characteristics of unexpected uterine sarcoma after hysterectomy and myomectomy for uterine fibroids: a retrospective study of 10,248 cases. Onco Targets Ther. 2015;8:2943-8. doi: 10.2147/ott.s92978 PMID: 26508879

153. Picerno TM, Wasson MN, Gonzalez Rios AR, et al. Morcellation and the Incidence of Occult Uterine Malignancy: A Dual-Institution Review. Int J Gynecol Cancer. 2016 Jan;26(1):149-55. doi: 10.1097/igc.0000000000000558 PMID: 26332395

154. Brohl AS, Li L, Andikyan V, et al. Age-stratified risk of unexpected uterine sarcoma following surgery for presumed benign leiomyoma. Oncologist. 2015 Apr;20(4):433-9. doi: 10.1634/theoncologist.2014-0361 PMID: 25765878

155. Tan-Kim J, Hartzell KA, Reinsch CS, et al. Uterine sarcomas and parasitic myomas after laparoscopic hysterectomy with power morcellation. Am J Obstet Gynecol. 2015 May;212(5):594.e1-10. doi: 10.1016/j.ajog.2014.12.002 PMID: 25499259

156. Cormio G, Loizzi V, Ceci O, et al. Unsuspected diagnosis of uterine leiomyosarcoma after laparoscopic myomectomy. J Obstet Gynaecol. 2015 Feb;35(2):211-2. doi: 10.3109/01443615.2014.937332 PMID: 25057886

157. Zhang J, Zhang J, Dai Y, et al. Clinical characteristics and management experience of unexpected uterine sarcoma after myomectomy. Int J Gynaecol Obstet. 2015 Aug;130(2):195-9. doi: 10.1016/j.ijgo.2015.01.009 PMID: 26117552

158. Clark Donat L, Clark M, Tower AM, et al. Transvaginal morcellation. Jsls. 2015 Apr-Jun;19(2). doi: 10.4293/jsls.2014.00255 PMID: 26005318

159. Bojahr B, De Wilde RL, Tchartchian G. Malignancy rate of 10,731 uteri morcellated during laparoscopic supracervical hysterectomy (LASH). Arch Gynecol Obstet. 2015 Sep;292(3):665-72. doi: 10.1007/s00404-015-3696-z PMID: 25820974

160. Lieng M, Berner E, Busund B. Risk of morcellation of uterine leiomyosarcomas in laparoscopic supracervical hysterectomy and laparoscopic myomectomy, a retrospective trial including 4791 women. J Minim Invasive Gynecol. 2015 Mar-Apr;22(3):410-4. doi: 10.1016/j.jmig.2014.10.022 PMID: 25460521

161. Brown J, Taylor K, Ramirez PT, et al. Laparoscopic supracervical hysterectomy with morcellation: should it stay or should it go? J Minim Invasive Gynecol. 2015 Feb;22(2):185-92. doi: 10.1016/j.jmig.2014.09.005 PMID: 25242233

162. American Cancer Society. Uterine Sarcoma: Key Statistics. 2016. Available at http://www.cancer.org/cancer/uterinesarcoma/detailedguide/uterine-sarcoma-key-statistics. Accessed on July 2016.

163. Graebe K, Garcia-Soto A, Aziz M, et al. Incidental power morcellation of malignancy: A retrospective cohort study. Gynecol Oncol. 2015 Feb;136(2):274-7. doi: 10.1016/j.ygyno.2014.11.018 PMID: 25740603

164. Tan-Kim J, Hartzell KA, Reinsch CS, et al. Uterine sarcomas and parasitic myomas after laparoscopic hysterectomy with power morcellation. Am J Obstet Gynecol. 2014 Dec 11. doi: 10.1016/j.ajog.2014.12.002 PMID: 25499259

165. Oduyebo T, Rauh-Hain AJ, Meserve EE, et al. The value of re-exploration in patients with inadvertently morcellated uterine sarcoma. Gynecol Oncol. 2014 Feb;132(2):360-5. doi: 10.1016/j.ygyno.2013.11.024 PMID: 24296345

166. Seidman MA, Oduyebo T, Muto MG, et al. Peritoneal dissemination complicating morcellation of uterine mesenchymal neoplasms. PLoS One. 2012;7(11):e50058. doi: 10.1371/journal.pone.0050058 PMID: 23189178

167. Sinha R, Hegde A, Mahajan C, et al. Laparoscopic myomectomy: do size, number, and location of the myomas form limiting factors for laparoscopic myomectomy? J Minim Invasive Gynecol. 2008 May-Jun;15(3):292-300. doi: 10.1016/j.jmig.2008.01.009 PMID: 18439500

168. Einstein MH, Barakat RR, Chi DS, et al. Management of uterine malignancy found incidentally after supracervical hysterectomy or uterine morcellation for presumed benign disease. Int J Gynecol Cancer. 2008 Sep-Oct;18(5):1065-70. doi: 10.1111/j.1525-1438.2007.01126.x PMID: 17986239

169. Takamizawa S, Minakami H, Usui R, et al. Risk of complications and uterine malignancies in women undergoing hysterectomy for presumed benign leiomyomas. Gynecol Obstet Invest. 1999;48(3):193-6. doi: 10172 PMID: 10545745

170. Theben JU, Schellong AR, Altgassen C, et al. Unexpected malignancies after laparoscopic-assisted supracervical hysterectomies (LASH): an analysis of 1,584 LASH cases. Arch Gynecol Obstet. 2013 Mar;287(3):455-62. doi: 10.1007/s00404-012-2559-0 PMID: 23053310

171. Kamikabeya TS, Etchebehere RM, Nomelini RS, et al. Gynecological malignant neoplasias diagnosed after hysterectomy performed for leiomyoma in a university hospital. Eur J Gynaecol Oncol. 2010;31(6):651-3 PMID: 21319509

172. Tan A, Salfinger S, Tan J, et al. Morcellation of occult uterine malignancies: an Australian single institution retrospective study. Aust N Z J Obstet Gynaecol. 2015 Oct;55(5):503-6. doi: 10.1111/ajo.12401 PMID: 26314239

173. Lin KH, Torng PL, Tsai KH, et al. Clinical outcome affected by tumor morcellation in unexpected early uterine leiomyosarcoma. Taiwan J Obstet Gynecol. 2015 Apr;54(2):172-7. doi: 10.1016/j.tjog.2015.03.001 PMID: 25951723

174. Park JY, Park SK, Kim DY, et al. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. Gynecol Oncol. 2011 Aug;122(2):255-9. doi: 10.1016/j.ygyno.2011.04.021 PMID: 21565389

175. Perri T, Korach J, Sadetzki S, et al. Uterine leiomyosarcoma: does the primary surgical procedure matter? Int J Gynecol Cancer. 2009 Feb;19(2):257-60. doi: 10.1111/IGC.0b013e31819a1f8f PMID: 19396005

176. Morice P, Rodriguez A, Rey A, et al. Prognostic value of initial surgical procedure for patients with uterine sarcoma: analysis of 123 patients. Eur J Gynaecol Oncol. 2003;24(3-4):237-40 PMID: 12807231

177. Pritts EA, Parker WH, Brown J, et al. Outcome of occult uterine leiomyosarcoma after surgery for presumed uterine fibroids: a systematic review. J Minim Invasive Gynecol. 2015 Jan;22(1):26-33. doi: 10.1016/j.jmig.2014.08.781 PMID: 25193444

178. Nannapaneni P, Naik R, de Barros Lopes A, et al. Intra-abdominal bleed following LLETZ. J Obstet Gynaecol. 2002 Jan;22(1):99-100 PMID: 12521750

179. Moroni RM, Martins WP, Ferriani RA, et al. Add-back therapy with GnRH analogues for uterine fibroids. Cochrane Database Syst Rev. 2015 Mar 20;3:Cd010854. doi: 10.1002/14651858.CD010854.pub2 PMID: 25793972

180. Gupta JK, Sinha A, Lumsden MA, et al. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev. 2014;12:Cd005073. doi: 10.1002/14651858.CD005073.pub4 PMID: 25541260

181. Peitsidis P, Koukoulomati A. Tranexamic acid for the management of uterine fibroid tumors: A systematic review of the current evidence. World J Clin Cases. 2014 Dec 16;2(12):893-8. doi: 10.12998/wjcc.v2.i12.893 PMID: 25516866

182. Bhave Chittawar P, Franik S, Pouwer AW, et al. Minimally invasive surgical techniques versus open myomectomy for uterine fibroids. Cochrane Database Syst Rev. 2014;10:Cd004638. doi: 10.1002/14651858.CD004638.pub3 PMID: 25331441

183. Panagiotopoulou N, Nethra S, Karavolos S, et al. Uterine-sparing minimally invasive interventions in women with uterine fibroids: a systematic review and indirect treatment comparison meta-analysis. Acta Obstet Gynecol Scand. 2014 Sep;93(9):858-67. doi: 10.1111/aogs.12441 PMID: 24909191

184. Jiang W, Shen Q, Chen M, et al. Levonorgestrel-releasing intrauterine system use in premenopausal women with symptomatic uterine leiomyoma: a systematic review. Steroids. 2014 Aug;86:69-78. doi: 10.1016/j.steroids.2014.05.002 PMID: 24832215

185. Clark NA, Mumford SL, Segars JH. Reproductive impact of MRI-guided focused ultrasound surgery for fibroids: a systematic review of the evidence. Curr Opin Obstet Gynecol. 2014 Jun;26(3):151-61. doi: 10.1097/gco.0000000000000070 PMID: 24751998

186. Kamath MS, Kalampokas EE, Kalampokas TE. Use of GnRH analogues pre-operatively for hysteroscopic resection of submucous fibroids: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2014 Jun;177:11-8. doi: 10.1016/j.ejogrb.2014.03.009 PMID: 24702901

187. Das R, Champaneria R, Daniels JP, et al. Comparison of embolic agents used in uterine artery embolisation: a systematic review and meta-analysis. Cardiovasc Intervent Radiol. 2014 Oct;37(5):1179-90. doi: 10.1007/s00270-013-0790-0 PMID: 24305981

188. Song H, Lu D, Navaratnam K, et al. Aromatase inhibitors for uterine fibroids. Cochrane Database Syst Rev. 2013;10:Cd009505. doi: 10.1002/14651858.CD009505.pub2 PMID: 24151065

189. Gizzo S, Saccardi C, Patrelli TS, et al. Magnetic resonance-guided focused ultrasound myomectomy: safety, efficacy, subsequent fertility and quality-of-life improvements, a systematic review. Reprod Sci. 2014 Apr;21(4):465-76. doi: 10.1177/1933719113497289 PMID: 23868442

190. Sangkomkamhang US, Lumbiganon P, Laopaiboon M, et al. Progestogens or progestogen-releasing intrauterine systems for uterine fibroids. Cochrane Database Syst Rev. 2013;2:Cd008994. doi: 10.1002/14651858.CD008994.pub2 PMID: 23450594

191. Martin J, Bhanot K, Athreya S. Complications and reinterventions in uterine artery embolization for symptomatic uterine fibroids: a literature review and meta analysis. Cardiovasc Intervent Radiol. 2013 Apr;36(2):395-402. doi: 10.1007/s00270-012-0505-y PMID: 23152035

192. Toor SS, Jaberi A, Macdonald DB, et al. Complication rates and effectiveness of uterine artery embolization in the treatment of symptomatic leiomyomas: a systematic review and meta-analysis. AJR Am J Roentgenol. 2012 Nov;199(5):1153-63. doi: 10.2214/ajr.11.8362 PMID: 23096193

193. Deng L, Wu T, Chen XY, et al. Selective estrogen receptor modulators (SERMs) for uterine leiomyomas. Cochrane Database Syst Rev. 2012;10:Cd005287. doi: 10.1002/14651858.CD005287.pub4 PMID: 23076912

194. van der Kooij SM, Bipat S, Hehenkamp WJ, et al. Uterine artery embolization versus surgery in the treatment of symptomatic fibroids: a systematic review and metaanalysis. Am J Obstet Gynecol. 2011 Oct;205(4):317.e1-18. doi: 10.1016/j.ajog.2011.03.016 PMID: 21641570

195. Chen I, Motan T, Kiddoo D. Gonadotropin-releasing hormone agonist in laparoscopic myomectomy: systematic review and meta-analysis of randomized controlled trials. J Minim Invasive Gynecol. 2011 May-Jun;18(3):303-9. doi: 10.1016/j.jmig.2011.02.010 PMID: 21545958

196. Yi YX, Zhang W, Guo WR, et al. Meta-analysis: the comparison of clinical results between vaginal and laparoscopic myomectomy. Arch Gynecol Obstet. 2011 Jun;283(6):1275-89. doi: 10.1007/s00404-011-1836-7 PMID: 21234758

197. Zapata LB, Whiteman MK, Tepper NK, et al. Intrauterine device use among women with uterine fibroids: a systematic review. Contraception. 2010 Jul;82(1):41-55. doi: 10.1016/j.contraception.2010.02.011 PMID: 20682142

198. Varma R, Sinha D, Gupta JK. Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS)--a systematic enquiry and overview. Eur J Obstet Gynecol Reprod Biol. 2006 Mar 1;125(1):9-28. doi: 10.1016/j.ejogrb.2005.10.029 PMID: 16325993

199. Steinauer J, Pritts EA, Jackson R, et al. Systematic review of mifepristone for the treatment of uterine leiomyomata. Obstet Gynecol. 2004 Jun;103(6):1331-6. doi: 10.1097/01.AOG.0000127622.63269.8b PMID: 15172874

200. Nieboer TE, Johnson N, Lethaby A, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev. 2009(3):Cd003677. doi: 10.1002/14651858.CD003677.pub4 PMID: 19588344

201. Metwally M, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. Cochrane Database Syst Rev. 2012;11:Cd003857. doi: 10.1002/14651858.CD003857.pub3 PMID: 23152222

202. American Cancer Society. Uterine Sarcoma: Survival Rates for Uterine Sarcoma by Stage. 2016. Available at http://www.cancer.org/cancer/uterinesarcoma/detailedguide/uterine-sarcoma-survival-rates. Accessed on July 2016.

203. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. Cancer. 1993 Feb 15;71(4 Suppl):1702-9 PMID: 8381710

204. Rose PG, Piver MS, Tsukada Y, et al. Patterns of metastasis in uterine sarcoma. An autopsy study. Cancer. 1989 Mar 1;63(5):935-8 PMID: 2914299

205. Harris JA, Swenson CW, Uppal S, et al. Practice patterns and postoperative complications before and after US Food and Drug Administration safety communication on power morcellation. Am J Obstet Gynecol. 2016 Jan;214(1):98.e1-.e13. doi: 10.1016/j.ajog.2015.08.047 PMID: 26314519

206. Parker WH, Kaunitz AM, Pritts EA, et al. U.S. Food and Drug Administration's Guidance Regarding Morcellation of Leiomyomas: Well-Intentioned, But Is It Harmful for Women? Obstet Gynecol. 2016 Jan;127(1):18-22. doi: 10.1097/aog.0000000000001157 PMID: 26646134

207. Juni P, Holenstein F, Sterne J, et al. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol. 2002 Feb;31(1):115-23 PMID: 11914306

208. Moher D, Pham B, Klassen TP, et al. What contributions do languages other than English make on the results of meta-analyses? J Clin Epidemiol. 2000 Sep;53(9):964-72 PMID: 11004423